

ANNUAL REPORT
OF
PROGRAM ACTIVITIES
DIVISION OF COMPUTER RESEARCH
AND TECHNOLOGY
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES
FISCAL YEAR 1974

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

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ANNUAL REPORT

OF

PROGRAM ACTIVITIES

U.S. NATIONAL INSTITUTE OF HEALTH, DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

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Fiscal Year 1974

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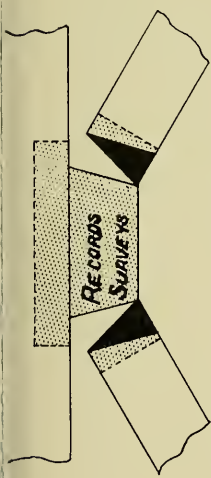
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PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY
Report of Program Activities
July 1, 1973 through June 30, 1974.

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ANNUAL REPORT

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DCRT Annual Report
July 1, 1973 through June 30, 1974
Office of the Director

It has been ten years since DHEW approved the concept of a new NIH division to cope with computers and to help reap the many benefits anticipated from "the broad application of this new technology to research in the life sciences." The FY1974 activities of the Division of Computer Research and Technology, set forth in detail by the laboratories and branches in this annual report, show the concept was prophetic and is still essentially sound.

This Director's Summary highlights these activities briefly and speaks to the future, wherein lie the opportunities and problems for computing at NIH. Four figures provide a visual FY74 synopsis of the size and functions of the DCRT components and the management and revolving fund expenditures, as well as a multi-year overview of growth in the NIH computer centers task load and in the revolving fund services rendered.

The Past Year

Computer Center Branch continues to provide NIH with responsive, reliable computing services and facilities of unexcelled quality and diversity. Use of both central systems (the IBM 360/370 system and the Digital Equipment Corporation (DEC) PDP-10 system) grew (now more than 200,000 jobs per month). Costs per user job were cut 30% or more. Major hardware improvements were installed on the DEC system and planned for the IBM system. Major software (systems programs) improvements were made on both.

What is important to emphasize here is the fact that growth in quality, quantity, sophistication and efficiency of the system and in economy and ease for the users has continued year after year. The ability to maintain and improve integrated man-machine-software systems of this magnitude is significant and of fundamental importance to NIH program activities. A dramatic example of the breadth of system capability is its application to store and analyze x-ray crystallographic data then to depict macromolecular configurations in 3D stereo, and finally to create by computer output an inexpensive microfilm stereo atlas of protein molecules for biochemists throughout the world. (This can be examined with a simple polarized viewer on conventional microfiche readers.)

The Data Management Branch is equally impressive in its area, i.e., designing and creating computer programs to manage and analyze data from scientific and administrative activities throughout NIH. In this way the Branch transforms the basic computing system power into useful work. The "application programs" are then owned and operated by the NIH scientific or administrative staff who have responsibility for the data. (The Branch also develops "software support" tools to speed the construction of their applications programs.)

Even though the DMB report is impressive, listing almost a hundred projects in FY74 for the great majority of NIH institutes and divisions, it understates the Branch's impact on NIH activities. It does not depict the many applications built in previous years and still functioning well throughout NIH. The cumulative effect over the last several years has greatly strengthened the useful application of computers in virtually all parts of NIH.

The Computer Systems Laboratory must be viewed from a different perspective. The laboratory develops computer systems for those activities at NIH which need something beyond the power of the NIH central facility. As the CSL report notes, these are mostly applications wherein the requirements for data acquisition, analysis and response require a dedicated or locally shared computer.

The CSL domain therefore includes the design, procurement, development, testing and installation of smaller computers and of their electronic interfaces, systems software and applications programs. The results are not measured in hundreds or hundreds of thousands of jobs per year but rather a few projects which each typically span several years from genesis to completion.

The CSL also has its cumulative impact through systems completed in prior years. Much of the CSL effort in FY74, as in the previous year, went into projects in support of clinical care, particularly the intensive care unit for heart surgery patients and the NIH clinical laboratories. Two new projects begun this year demonstrate that there continue to be entirely new applications for electronic engineering and computer hardware expertise in NIH biomedical research.

The Laboratory of Applied Studies represents another part of the spectrum of DCRT disciplines, which extends across computer technology, engineering, applied mathematics and their uses in biomedicine at NIH. The LAS report notes that its primary emphasis is on direct application of mathematics and statistics. In addition, LAS does research in these fields. Its bibliography shows that both endeavors are productive.

Indeed, the LAS work illustrates within the DCRT the breadth of computing throughout the NIH. In FY74 the LAS staff worked in electrocardiology, nuclear medicine, biochemistry, neural modeling (computer and mathematical) microcirculatory modeling, hardware and software systems for data analysis and a variety of other projects. These involved extensive collaboration with other parts of DCRT as well as with many NIH laboratories and branches and with coworkers outside of the NIH. They use computing resources selectively but in a fashion which demonstrates need for the full breadth of disciplines originally specified for the division a decade ago.

The Physical Sciences Laboratory also applies mathematics broadly to the examination and elucidation of biomedical phenomena at a fundamental level. Its work on the theory of intermolecular forces in biochemical aggregation moved forward accompanied by the development of new experimental techniques to confirm the theoretical insights. Advances in nuclear magnetic resonance instrumentation, with computer control and analysis, led to new theoretical work on polypeptide coiling and new discoveries about the interaction of subatomic particles under varying biochemical configuration.

The PSL expertise carried to many other areas such as the dynamics of macromolecules, microorganisms and blood elements, the interpretation of kinetic biochemical analysis and the design of clinical trials. The PSL bibliography speaks to the productive collaboration of this group with investigators in other NIH laboratories.

The Heuristics Laboratory applied computing methodology to information handling and analysis for a wide variety of topics, extending its fundamental work on theorem proving to computer program verification and its pattern recognition efforts to liver disease cases, mass spectral data and tissue-typing screens. Its previous collaborative efforts in developing mass spectral data file searching systems now have international recognition and sponsorship and it began collaboration on design of a more flexible and powerful system for the Walter Reed (Army) chemical substructure search system.

The HL work on data analysis and modeling saw many new users for the MLAB system, a more sophisticated approach to linear multiple regression analysis, and the development of an improved simulation model for an NICHD menstrual cycle model. Its bibliography also testifies to active collaboration with investigators in other NIH laboratories.

The Present

A prime influence on the DCRT at present are the personnel limitations imposed as part of the ceilings placed upon the NIH. Cuts in budgeted and actual DCRT positions have come progressively, during the very years when its new Laboratories and Branches matured, became more productive and engaged fully with the rest of the NIH. The division absorbed these cuts and the remaining staff overcame them with increased individual effort and more effective use of computational power and sophistication. But in FY74 perennial retrenchment finally forced a reorganization and withdrawal from a DCRT commitment to those fundamental efforts embodied in its Heuristics Laboratory.

The particular irony of such a necessity can only be appreciated by viewing the course foreseen by those who created the division a decade ago. The Steering Committee in 1963 declared: "The measure of the Division's success will be the extent to which it stimulates the introduction of ADP methodology into on-going programs." Computing facilities and services, data processing capabilities, computer system engineering and the application of modern mathematics to biomedicine have become a functional reality in the daily life of the NIH. Now is the very time when the mathematical and information handling research base should start making its greatest contribution to the NIH mission, but it is the very time at which this base had to be cut.

The Future

The DCRT commitment is fundamental support of effective computing in NIH programs. To this end and under the reality of FY74 cuts, a new DCRT laboratory was initiated this year, drawing expertise from several other parts of the division. This laboratory will contain a multidisciplinary nucleus of professionals in contact with the developments outside NIH, and like other DCRT laboratories it will do research. But its prime responsibility will be to bring modern computer based capabilities in data analysis, mathematical statistics and other mathematical methods closer to biomedicine in the NIH programs, both by its own activities and by support of biometry in other parts of NIH.

At this time, moreover, extensive involvement of the DCRT program as a whole in NIH program activities forbids any further reduction of effort in any DCRT

laboratories and branches, if the fundamental DCRT commitment is to continue without loss of effectiveness and momentum. The original 1963 prospectus for "the computer division" envisioned growth from 335 employees in FY1965 to 680 in FY1969. This prophecy may have been unrealistic, but it foretold the need for some new activity as the promise of computing became fulfilled in NIH programs. Computing is now making steady strides in medicine, biomedical research and management. The fundamental strategy for the NIH must be to defend its carefully developed computing base against further retrenchment or retrogressive influences.

The danger appears nowhere more clearly than the threats to the basic NIH computer capabilities posed by some administrative philosophies at other Federal levels. The technical expertise and managerial acumen which developed the central NIH hardware/software systems has been unexcelled, if indeed matched, elsewhere in the Federal establishment. In large measure this is true because the NIH leadership understood the complexity of computing in the NIH environment and delegated responsibility to the level where the requisite technical expertise and managerial experience could be established. Continued knowledgeable support by the NIH leadership will be needed to prevent erosion of the strength and effectiveness by external administrative requirements which lag behind the current technology and are virtually inapplicable to the complex, multiprocessing, multiprogramming, multidisciplinary NIH environment.

The Steering Committee Report in 1963 identified this basic problem in its discussion of computing in the governmental setting: "Government installations, particularly Federal scientific laboratories, seem to have encountered more serious problems than either universities or industrial centers. Administrative policies have been formulated with undue consideration to the use of computers for business or administrative applications." In spite of recognized competence and leadership, the DCRT and NIH carry a continual burden of educating others about the NIH program requirements.

The need is for establishment of the historical perspectives and the prospective understanding which will allow NIH on-going programs to continue to benefit fully from the technology now that it has been introduced. The Steering Committee words in 1963 are again worth noting: "The present Committee was impressed by the fact that the conclusions it reached after protracted analysis, and which are embodied in this report, constitute, in terms of broad outlook and major thrust, another step in a continuum first articulated almost a decade ago."

Recognition of the continuum and its progression is as important as appreciation of the accomplishments of a single year. Electronic computing is a little more than halfway through its second decade at NIH. It is currently a very considerable success due to previous foresight and enterprise. The degree of success today does not reduce the need for foresight today and enterprise tomorrow.

REVOLVING FUND -
DIVISION OF COMPUTER RESEARCH & TECHNOLOGY

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DIVISION OF COMPUTER RESEARCH & TECHNOLOGY

PROPORTIONAL REPRESENTATION OF EXPENDITURES - FY19/14 (est.)

MANAGEMENT FUND

90	PFT POSITIONS
\$1,972	LABOR COST
1,094	OTHER
1,435	DATA PROCESSING
\$4,501	TOTAL

REVOLVING FUND

171	PFT POSITIONS
\$ 2,777	LABOR COST
10,756	OTHER
\$13,533	TOTAL

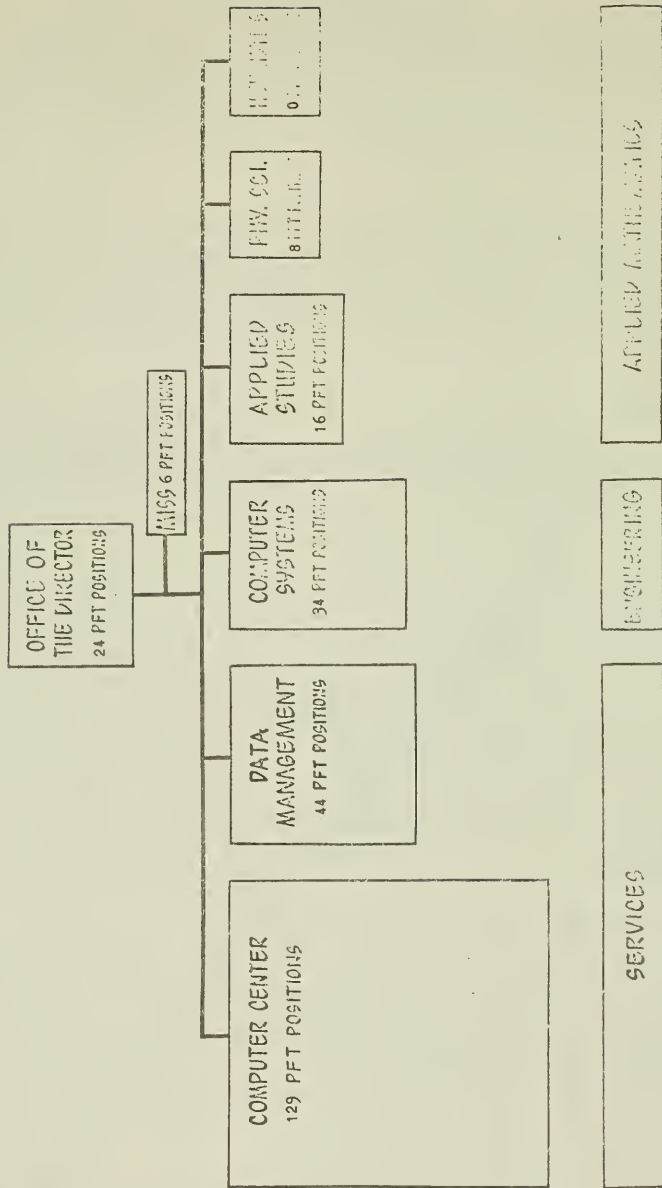
PROFIT

\$556 TOTAL

\$1.2 MILLION REBATE

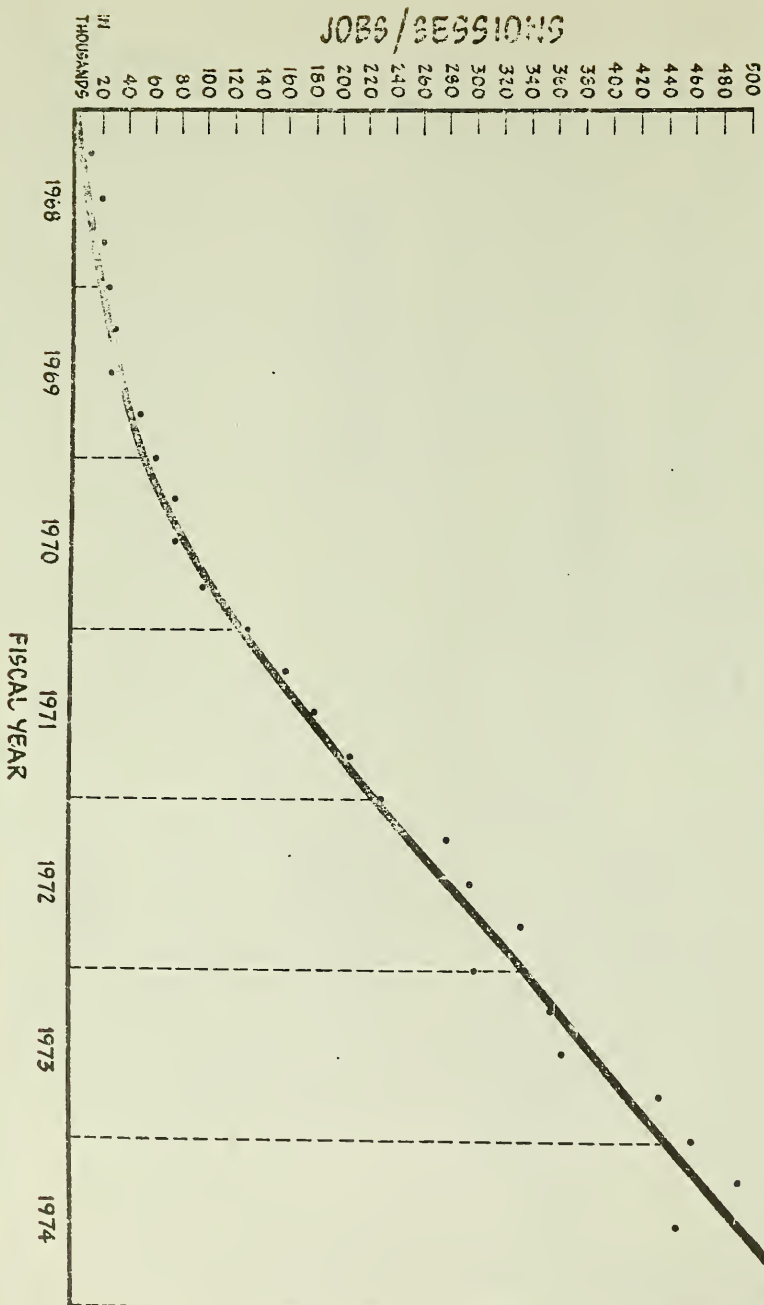
DIVISION OF COMPUTER RESEARCH & TRAINING

PROPORTIONAL REPRESENTATION OF STAFF - FY1974



DIVISION OF COMPUTER RESEARCH & TECHNOLOGY

COMPUTER WORKLOAD



Summary of the Associate Director

July 1, 1973 through June 30, 1974

The DCRT Scientific and Technical Information Office (STIO) became involved by error in the departmental attack on public relations puffery. Fortunately the basic duties of the STIO, set forth in 1970, were clear and dispelled the error quickly. The new emphasis on "inquiries" and "reports" fits the established STIO functions.

The implication that "information" is henceforth a dirty word in DHEW may pose semantic problems for DCRT. Computers are, after all, information processing machines; information processing, with or without computers, is a large part of the NIH job; and the STIO has a functional responsibility for "communication" of information about the processing of biomedical data by computer based techniques. This function amounts to more than answering inquiries and generating reports.

The STIO edited and published two DCRT Technical Reports during the year: No. 9, A Structured Assembly Language Source Program Generator and No. 10, The Carcinogenesis Bioassay Data System. Both describe systems developed within our Data Management Branch. The office set up a standing Review Committee, composed of representatives of each Lab and Branch, to support standards of style and substance in the Technical Report series.

The office continued to receive and answer inquiries from outside NIH. In the main, these ask about medical applications, careers in computing and specific computer software or scientific information centers. The office arranged formal visits for two national organizations: The American Medical Writers Association and The National Association of Medical Explorers. To answer questions of visitors to the Computer Center and to other parts of DCRT, the STIO designed an exhibit in conjunction with Medical Arts and Photography, DRS, and installed it in the lobby between Buildings 12 and 12A. It contains short "reports" about the functions of the Division and its Laboratories and Branches. A fuller set of brief reports on DCRT components and activities is planned, partly for this exhibit but equally important for rapid and effective briefings of the many technical and managerial visitors who come to DCRT from many parts of the world and the Federal government.

More extensive specific reports for the NIH staff have been suggested. The STIO distributed a bulletin of recent DCRT library acquisitions and technical reports to NIH scientists and administrators at the Lab and Branch level. The items were a sample deliberately selected to explore interests in a wide range of managerial and scientific computing topics. Most responses were requests for technical materials which are already routinely announced. The bulletin was discontinued and more direct approaches will be used to direct readers to DCRT library acquisitions and to find out the topics of major interest for special reports.

As in previous years, the office was responsible for many recurring administrative reports, clearances and archival functions in support of Division programs.

The DCRT Library strengthened its collection of documents in computer science and related fields, adding about 200 new books and 100 technical reports. Five new periodicals were added and four were cancelled or ceased publication. The library continues as a unique resource for NIH and for many scientific or technical workers in the Washington area. Almost half of those who borrowed books were not DCRT staff.

Library operations were enhanced by a new automated circulation record system, adapted from that developed for the EPA library. It has been used for a year and supports our circulation policy very successfully by permitting borrowers to keep books for an extended period and at the same time quickly and efficiently locating books when they are needed by other users. Borrowers periodically receive a listing of materials checked out to them, making it easy for them to keep track of and return their individual holdings.

The library added the NLM MEDLINE to its services on a trial basis. The response was promising, with very active use during the first two months of 1974 by medical students in the "Computers in Clinical Medicine" elective. A terminal is planned in the library when a telephone line becomes available. This should stimulate more use of the system. The STIO will undertake an evaluation of its utility as an information service in our environment.

For the coming year we are considering (1) a survey to eliminate unused journals, (2) weeding the monograph collection to discard outdated materials, (3) further development of an in-house training program for the library assistant and (4) additional automation of selected library functions.

The Computers in Clinical Medicine elective was given for the third year as part of the NIH Clinical Elective program for medical students. For the first time it incorporated a two day seminar with invited experts, Drs. Howard Bleich, Jerome Cox, William Yamamoto and Homer Warner. This addition was quite successful, in large part because of the high quality of the students. Several students from this and previous years intend to return to NIH for Associate positions. The elective does, however, place a considerable load on DCRT and other NIH staff, and it will undergo a detailed evaluation and possible redesign before it is offered again.

Summary of the Assistant Director

July 1, 1973 through June 30, 1974

The Office of the Assistant Director, DCRT, provides four basic capabilities:

1. It serves NIH as the focus for NIH-wide coordination of ADP policy matters.
2. It serves NIH as a central point of contact with PHS, the Office of the Secretary, other DHEW agencies, GSA and OMB, relative to NIH ADP policy questions.
3. It supports the Director of DCRT by providing a point of reference and coordination to insure that DCRT's own ADP activities are consistent with NIH, PHS, O/S, GSA and OMB policy directions, and
4. It supports the Director of DCRT by providing advice on resource acquisition and allocation necessary for DCRT to support the above functions.

The coordination role is most often exercised in connection with the fact that all proposals for contracts or procurement actions involving ADP equipment, services, programming or design are cleared through this office prior to being executed. This provides a continuous opportunity to alert program or contract officials to opportunities to reduce costs and/or avoid duplications and to avoid difficulties with higher echelons.

During FY74 extensive assistance was, for example, provided to ODA/NIH to develop an RFP, evaluate proposals and negotiate a \$304,310.00 contract to develop a single comprehensive Material Management System for NIH. Our support of NCI's effort to develop a primary Cancer Research Center at Fort Detrick in Frederick, Maryland, continued. Significant unnecessary costs were avoided and capabilities improved by arranging for the prime contractor at Fort Detrick to himself develop an ADP capability in lieu of subcontracting. Assistance was provided to the National Library of Medicine in beginning the long process of obtaining PHS, OS and GSA approval for a major ADP hardware upgrade.

A major undertaking started during FY73 but continuing into FY74 was the technical and management leadership for NIH's effort to develop its second comprehensive ADP Plan. This plan, now an annual effort, attempts to lay out a two year projection for ADP equipment, manpower, contracts and business data systems for all components of NIH. This planning process creates an orderly opportunity for ADP users to take stock of their goals and accomplishments. The second annual plan covered NIH ADP efforts exceeding \$31 million for FY74. An NIH wide study of systems handling data concerning NIH grants was a direct result of apparent duplication and overlaps detected during the planning cycle. Work on the third annual plan, that for FY75, was underway at the close of the period covered by this report.

In serving as a central point of contact for NIH on ADP related matters with PHS, DHEW, GSA, OMB, etc., a large number of NIH research and research support staff members are spared the agony of becoming expert in the many nuances of ADP management regulations. Since these regulations are generally written from a second generation business data processing point of view, a thorough understanding of their purpose and operation often allows beneficial interpretations of their application to the NIH research environment.

During FY74 the PHS was recreated including an ADP Policy Office. The Assistant Director continues to provide extensive assistance to PHS to attempt to mold that office into an entity which can be helpful to NIH rather than becoming a hindrance. The Office of the Assistant Director lent extensive help to a study, commissioned by the Executive Officer, PHS, that resulted in a major PHS decision to consolidate all Parklawn ADP facilities. Under the guidance of the Office of Assistant Director, a systems study and a draft RFP were developed to allow an upgrade of DCRT's PDP-10 image Processing Computing Facility. Similar efforts were started regarding the main DCRT operated NIH central facility.

As regards DCRT's own operation, the Office of the Assistant Director coordinates all ADP procurements, contracts and work orders which have a technical or engineering impact on our computer operations. By bringing an understanding of technical considerations into these matters, better and more responsive services are obtained from the central service groups. During FY74 the initial phases of two major physical site changes were coordinated. One is an addition to Building 12 to provide storage space and relocate office space. The second will be a gradual conversion of the second floor of Building 12 to machine space.

July 1, 1973 thru June 30, 1974

PUBLIC HEALTH SERVICE-NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

2. COMPUTER CENTER BRANCH

1. DCRT-2
Serial Number
3. J. D. Naughton
Branch Chief

MISSION

The Computer Center Branch designs, implements and operates a large general-purpose computer utility to meet most effectively the dynamic and diverse requirements of both N.I.H. research investigators and managers in the support of modern medicine. This charge includes the original development of new system facilities to meet the unique requirements of the NIH mission in order to bring the full power of the computer to bear on problems at every level of biomedical research in many diverse locations. The core of this computer utility is a network of computers and remotely located terminals, which, by means of a modern communications network, extends the power of the computer directly into research laboratories and administration offices throughout N.I.H. This provides immediate access to the computer from thus minimizing delays in the research program and making more efficient use of critical manpower than more traditional methods. An inherent responsibility of the Computer Center is the continued research and development of new methods to extend the network even further into the research environment while continually adapting to the constant impact of new knowledge and program direction.

A full spectrum of computational services is provided to all Institutes and Divisions of the NIH on a fee-for-service (cost recovery) basis. These facilities include conversational programming, graphics, microfilm output, text editing, remote job entry, time sharing, data base management and batch processing. Large systems as well as mini-computers and terminals are tied together providing a "distributed capacity" available at many levels. Research into the computer and information sciences coupled with close cooperation between the N.I.H. medical investigators and the computer scientist have introduced computers directly into the research environment where they can perform most effectively in attacking the complex problems of medical research.

The medical research programs of N.I.H. require the most powerful and flexible of computer services and tools available today. The computer network provided must have a distributive power that is easily accessible when needed to scientists in the laboratory itself. The goal is to mold, polish and, in general,

enhance the computer into a complete tool for medical research and its administrative support. New areas of computer applications are sought out continuously in conjunction with a comprehensive training program to inform research investigators of the latest methods in the use of computers to most effectively meet the unique requirements of their individual laboratories.

1974 ACTIVITIES

Throughout 1973, users of the NIH Computer Center continued to demonstrate outstanding innovation in the application of all computational services to the mission of the agency. Users rapidly adapted existing programs to take maximum advantage of new time-sharing services as they became available and continued to develop a never ending stream of new programs using traditional batch processing services.

The overall workload of the Center continued to increase at its normal growth rate of 25% per year for the seventh consecutive year. The use of batch processing services increased throughout the year to a workload of 3,200 jobs per day with over 80% of them being completed with results available to the user in less than two hours.

The use of interactive terminal systems (WYLBUR, TSO, and CPS) experienced the most dramatic increase (33%) to over 2,500 sessions per day. A new record for the number of simultaneous WYLBUR users was set at 189 in April while the new TSO service established its first plateau of 36 simultaneous users. As the number of keyboard terminals using the NIH Computer Utility grew to 800, the number of telephone lines accessible to the system was increased to over 250 to minimize the frequency of busy signals received when dialing the interactive services.

The current workload, along with the projected increase in demand for services, has precipitated a system study addressing the problems of expanding the computational capacity of the system and improving response time for interactive services. This study has shown a need for significantly increased CPU power within the multi-processor utility. Procurement procedures are now being followed so the Computer Center can acquire the necessary capacity before service to the NIH community degenerates to an unacceptable level. The study has also identified a need for virtual hardware and its associated software techniques in order to maintain rapid response for the interactive terminal user. These techniques will also improve system efficiency and will eventually permit the relaxing of some technical constraints currently placed on users of the Utility. The study also identified the need for new telecommunication controllers to provide users the ability to

communicate with the system using CRT terminals at speeds of 1200 baud. The controller will also allow more efficient use of existing teleprocessing ports. A variety of terminals, operating at different speeds with different protocols, will all be able to call the same telephone number thus reducing the need for redundant system resources.

Increased workload, larger systems, and internal improvements on operating efficiency combined to permit the most significant rate reductions ever announced for users of the NIH Computer Center. Beginning January 1, 1974, both batch processing and terminal elapsed (logon) time rates were reduced 25-30% for all users of the Center. On that date, elapsed terminal time for all interactive systems, WYLBUR (MILTEN), TSO, CPS, CICS, and the DECsystem-10 were reduced 25% to the new rate of \$3.00 per hour. The batch processing rate experienced the most dramatic change. The basic machine unit rate for all classes of batch processing work was reduced a full 30% resulting in a new rate of \$1.70 per resource minute and the night processing differential was increased an additional 5% making it 25% cheaper to process work at night. Tape and disk mounting coefficients were adjusted resulting in an overall reduction of 6% for private tape and disk users.

These rate reductions were made possible primarily because of the constantly increasing demand for computational services from the many users of the NIH Computer Center. As the NIH Computer Utility expanded both in size and function to meet this demand, the economies of scale contributed significantly to reducing operating costs. Since the fixed costs and overhead of the system do not increase in direct proportion to its processing capacity, the effect is to reduce per unit costs even further. This represents the seventh consecutive year during which the NIH Computer Center has been able to offer rate reductions to its users.

Continuous efforts by the Computer Center Staff to improve the internal operating efficiency of the NIH Computer Utility also contributed significantly to reducing operating costs. Monitors were used extensively to tune the system to the unique characteristics of the NIH workload. Channels, disks, tapes, and unit record equipment were reconfigured to obtain maximum throughput. Older communications controllers were replaced by more modern units offering new functions as well as improved price/performance. Major parts of the operating system were modified extensively to gain improvements in internal performance as well as increased reliability and function.

In December the transfer of all interactive data lines to a newly installed "data switch" was begun in an effort to separate the data traffic from the overburdened NIH voice switchboard.

The system itself also received new communications controllers to provide increased accessibility to the system. During the year the number of batch RJE terminals entering the system increased substantially and their transmission rate was increased from 4,800 to 7,200 baud to allow higher speed remote printing. As of the close of the year, almost 93% of all work processed at the Center was received over the teleprocessing network.

As users developed new on-line data base applications the demand for on-line disk space increased dramatically. Additional FILE packs, PDS packs, TMP packs, work space packs, and private packs were added to the system in an attempt to meet this need. Over 7 billion bytes of directly addressable disk space contains over 80,000 users datasets on-line at all times; a necessity for effective use of interactive systems.

In an attempt to keep pace with the changing requirements of the NIH computer users, many past restrictions were eliminated or eased and new systems software facilities were implemented. The maximum allowable region size for all job classes was increased 50% to 300K bytes to permit the development of larger applications programs without the necessity for segmentation or overlays. A new disk mapping facility was developed to provide users with more detailed information on the type and status of their on-line datasets. A new tape copy utility was developed to allow users to copy entire tapes using minimal JCL. Facilities were provided to enable users to determine the amount of available free space on the on-line packs at any instant in time. The requirement that all procedures to be catalogued be carried to the PAL Unit was eliminated with the announcement that such procedures could be submitted via WYLBUR.

Users received individual assistance from the Computer Center staff on specific problems through written replies to 2,104 Programmer Trouble Reports (PTR) and through thousands of telephone calls and visits to the PAL unit for personal assistance. In an effort to minimize paper work for both the Center and users, and in an effort to provide more effective support to remotely located users, the PTR and Refund Request forms were combined into one and a facility for submitting the new form via TSO was offered. The requirement for special registration for CPS use was eliminated and CPS users were no longer restricted to the use of only one library.

WYLBUR was enhanced with the addition of many new and improved commands. TSO moved from an experimental test status to a full production system providing terminal I/O and interactive program development and debugging in FORTRAN, COBOL, PL/1, and Assembly Language. WYLBUR and CPS were then made available under the TSO monitor. Although TSO experienced some rather severe

performance problems when first installed, incremental improvements were made as the year progressed and additional improvement is planned for next year.

A major system project was initiated for the redesign of the popular conversational text-editor and remote job entry system, WYLBUR. The new design is based on the experience of the past five years. It will provide a more efficient system, having the ability to handle over 300 terminals simultaneously. New features will be added to the system. Many of these new features were based upon suggestions made by users over the past few years. New terminal types will be available at higher data rates and a powerful new macro-processing capability will be available. This will enhance the power of WYLBUR and enable it to operate efficiently in many new areas such as transaction oriented on-line data collection systems

The installation of Release 21.6 in June was the only operating system release change made in over a year, and the conversion was totally transparent to most of the user community. Those users who experienced the traumatic experiences of early release changes recognize the significant improvement in this area. Several compilers were replaced with newer versions fixing many old problems and adding new features. The PL/1 Optimizing Compiler replaced PL/1(F); FORTRAN G was retired in favor of FORTRAN G1 and ANS COBOL II gave way to ANS COBOL IV

One of the more significant accomplishments of the year was the design and implementation of an automatic dataset migration facility to both save money and make more on-line space available for users. During the first two months of its operation over 20,000 datasets were migrated to magnetic tape saving \$30,000 in storage charges and making 80,000 tracks of critically needed on-line space available for use.

As warnings of impending paper shortages were received, many NIH computer users converted programs to produce output on microfiche rather than the traditional and more costly printed page. Because of an overwhelming increase of over 200% in the use of microfiche during the year, a second unit was installed at year's end to support the increasing demand. A new software utility was provided to allow a programmer to conveniently direct the complete output of a job to microfiche.

The technical documentation and training activities of the Center continued to expand. The training program offered thirty-eight different courses and seminars during the Spring semester and forty in the Fall. Two new series of courses were included among the new offerings for the first time this year--a series on the use of TSO and an expanded DECsystem-10 programming sequence. Fourteen seminars extended the program

more deeply into the substance of the users problems. Over 1,940 student course applications were received this year from candidates of varying backgrounds, an increase of 5-1/2% from last year. Unfortunately, due to lack of qualified teaching manpower and classroom space, over 400 students had to be denied admittance.

As the number of users and functional capability of the NIH Computer Utility increased, the demand for current technical documentation increased correspondingly. The Technical Information Office distributed over 32,000 pieces of documentation, ranging from a one page WYLBUR reference card to a 418 page Computer Center Users Guide. Documentation profiles of 2,700 individual users were maintained by the Automatic Documentation Service to insure that all users received only the documentation relevant to their interest or needs. Many documents were completely revised and others received only minor corrections and enhancements.

The frequency of INTERFACE decreased slightly this year as only seven issues were published. These issues presented over 275 pages of technical documentation on the organization, policy, philosophy and use of the NIH Computer Center as well as basic concepts in computer science. Data Line continued to receive a number of provocative questions from users and provided informative answers (we hope). Programming Methods appeared regularly with discussions of varied programming techniques and concepts in computer science. The Bugs, Hints, and Diagnostics section continued to provide users the detailed technical information necessary to process work on the Utility. With the last issue of the year, the Compleat Computer expanded in purpose to include tutorials on subjects of general interest. The second annual index to INTERFACE covering all issues up through the end of 1973 was published.

The PDP-10 system, now designated as DECsystem-10, also underwent major transformations during the year. Early in the year the original KA-10 processor was replaced by a new paged dual processor KI-1077 processor with hardware double precision arithmetic, faster memories, triple the amount of on-line disk storage, fast swapping drums and additional peripherals.

This dual-processor system now provides additional capacity as well as processor redundancy permitting the system to remain operational even if one of its processors fails. The dual system is controlled by a new operating monitor which is capable of dynamically balancing the load between the two CPU's. The accessibility to the DECsystem-10 was increased by providing ports for both 2741 type interactive keyboard terminals and full duplex CRTs operating at 1200 baud.

The excellent Time-Sharing services of this system have been recognized by many scientifically oriented users. In particular, the constantly improving and evolving OMNIGRAPH system has proven to be of great and continuing interest to an ever growing group of graphics aficionados. A program named "PLOTX" provides the link between pictures seen on a scope and the hardcopy desired for research notebooks or formal publication.

Of particular interest to laboratories with their own smaller data acquisition systems was the design and implementation of software to permit a remote PDP-11 to be used as a terminal concentrator over a high-speed 9600 baud non-conditioned line. This system will handle up to 8 teletype devices with speeds up to 240 characters per second and is connected to a PDP-11 Synchronous Communications Processor which in turn is interfaced to the dual KI-1077 system.

The already extensive repertoire of available languages and programming tools was supplemented this year by 2 major additions: APL and SPSS. The former language is particularly suited for statisticians dealing with problems involving matrices and the latter is of interest to researchers with statistical problems. For those people who have need for special pre-printed forms or high volume printed output, a new facility was developed which permits the transfer of magnetic tapes containing upper-lower case text to the 370's for printing without the necessity of writing JCL.

The operating hours of the DECsystem-10 were expanded considerably during the year to provide more flexibility in working hours for users of the system. The system now has operator coverage 16 hours a day from Monday through Friday and 8 hours each Saturday. Even Sunday is now available by special request.

We are particularly pleased that the DECsystem-10 helped to save the life of a six-year old boy who had ingested an unknown poison. An EPA gas chromatograph-mass spectrometer was used to analyze the sample and the sample's spectrum was matched with the standard parathion profile using the system. The results of this search provided the basis for selecting the proper treatment.

The XRAY modeling system has become a routine part of the process of the determination of the structure and function of macro molecules. A number of papers, films, and seminars have resulted from the application of this system. Extensions to the system during the year included the capability of fitting molecular structures to electron density maps, and a means of determining the conformation of structure in the active site of a macro molecule using NMR data. In conjunction with modeling,

the crystal structure data base continued to develop and grow. The structures in the crystal data base can now be searched on bibliographic and structural terms. The resulting three dimensional coordinates of the structures are then manipulated using the XRAY system and displayed on a CRT for immediate review by the investigator.

The first phase of the Computer Center's planned efforts to protect the confidentiality of sensitive data, improve the physical security of the computer system, and prevent unauthorized use of account numbers became visible. In addition to the installation of locks on the machine room doors, two new software facilities were installed to provide data security. A data encoding system which scrambles sensitive data using a code phrase which is defined and known only to the user was made operational for all users. Another degree of security was achieved by improving the existing keyword facility and extending it to make the setting of a keyword effective for both batch and terminal systems. A number of additional improvements for security and confidentiality within the NIH Computer Utility are under development for installation in the coming year.

1975 PLANS

The high standards of performance and the outstanding reputation maintained by the NIH research community make it mandatory that the Computer Center continue to provide new computational capabilities to the NIH research administrative communities. New facilities plus the current high level of computational support are necessary for the success of the NIH mission. In the coming year plans have been made to increase the computational capacity of the NIH Computer Utility. This will keep the level of service at the desired plateau and provide us with virtual hardware, which will enable the Center to employ new virtual techniques in overcoming computational restrictions currently placed on the NIH research community. A comprehensive data base management system will be installed and put into general use. This will give users a powerful tool for data base management and rapid response to queries for specific information. An entirely new WYLBUR with many new and powerful features will be offered. The size of the on-line data storage will be increased significantly to meet the on-line space requirements of new applications. New terminal types will be investigated and the ones most appropriate for the NIH need will be offered to users. Programs for the correlation between crystallographic structure determination methods and NMR structure determination methods will be investigated. Work will continue in the fine tuning of the NIH Computer Utility to keep it responsive to the changing needs of NIH, and in the investigation of new computational techniques that will contribute most effectively to the support of the NIH mission.

July 1, 1973 through June 30, 1974

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

2. LABORATORY OF APPLIED STUDIES

1. DCRT - 3

3. Eugene K. Harris
Chief

The Laboratory of Applied Studies engages primarily in cooperative studies with NIH scientists, applying mathematics, statistics and computing science to biomedical problems. In addition, the Laboratory undertakes mathematical and statistical research with applications to biology.

During most of this reporting period, the Chief, LAS, has been on research assignment to the Medical Research Council of Great Britain, Clinical Research Centre, near London. The term of this assignment to the U. K. will conclude in August, 1974. Results will be forthcoming during the next reporting year and will be described in the next annual report.

The Head of the Biomathematics and Statistics Section has served as Acting Chief.

During this reporting year, the Medical Applications Section has completed evaluations of three computer programs for the interpretation of electrocardiograms. These results will appear in the July issue of Circulation. All routine adult electrocardiograms collected at the Clinical Center are currently being processed by one of the programs. After review by the cardiologist, the computer printout becomes the official ECG reading and is entered into the patients' charts.

Evaluation of ECG programs is continuing, and additional cases with clinical documentation are being collected by the Medical Cardiology Department of the Royal Glasgow Infirmary in Scotland. Performance of a program in routine use at NIH will be compared with that of a program developed in Glasgow. ECG data from Scotland, The Netherlands, and Sweden will be used in further testing and evaluation of programs.

Computer-based support of diagnostic and research activities of the Nuclear Medicine Branch of the Clinical Center was continued by the nuclear medicine task force consisting of personnel from both LAS and CSL of DCRT and those of NM, CC. The most important clinical application achieved in FY 74 is the development of ECG-gated scintiphotographic cine angiograms of the heart. This tool makes possible the non-invasive study of heart function in patients about to undergo cardiovascular surgery and in a follow-up period. Because of its non-invasive, non-traumatic character, requiring no anaesthesia and less radiation dose to the patient than a single chest X-ray, this study can safely be repeated frequently. Therefore, it shows considerable promise as a clinical tool.

Several other clinical applications including a scintigraphic evaluation of pulmonary function in pre-operative patients at NHLI are being studied.

Activities in the computer modeling of neurophysiological phenomena continued. These center around the LAS MAC-16 laboratory computer. A neural hardware model interfaced with the MAC-16 was used to study a small neural net and give insight into the manner in which an action potential can modify the shape and duration of post-synaptic potentials and their spatio-temporal interactions. The system was also used to model cerebellar function. Study of the reciprocal inhibition-excitation behavior of small neural nets continues.

Development of the MAC-16 laboratory research system continued. It has now been interfaced with the Marquette tape drive, used for analog recording of ECG's, the Honeywell 7600 analog tape transport, the neural control panel, the general purpose switch-filter network, and a real time spectrum analyzer with ensemble averager. With this system, the investigator can automatically pre-process (filter and/or digitize) -- his data so that he can get the most economic use of a large-scale digital computer.

In FY 74, the advantages of such pre-processing was demonstrated with cardiovascular data recorded on live monkeys, which enabled the investigators to study myocardial contractility and ECG reproducibility.

In collaboration with the National Institute of Occupational Safety and Health (NIOSH) analog data from vibratory equipment and the effect of this vibration on human electromyograms is being studied using the spectrum analyzer.

The Applied Mathematics Section has concentrated its efforts in two primary areas: (1) the mathematical modeling of biological processes, and (2) methodology and techniques for fitting models to data. The various aspects of these areas are described in detail in the following paragraphs.

Preliminary results from Oxygen Transport to Tissue Modeling have been presented at conferences and an extensive paper detailing the mathematical model has been submitted for publication. A number of simulation programs have been combined into a single program with options for a variety of physiological conditions. Further work in this area will be concerned with improved data on oxygen-hemoglobin dissociation reactions, autoregulatory effects of flow and tissue metabolism, and formulation of new concepts using time dependent flow fields.

An extensive investigation of the partition of long-chain fatty acids between n-heptane and an aqueous buffer has been completed, and the results are in press. Related studies continue.

The curve-fitting routines of MODELAIDE were revised, and a collaborative project with CCB and PSL was undertaken to adapt MODELAIDE for use from a Tektronix 4010 graphics terminal under the new Time Sharing Option (TSO). This system is now operational.

A number of algorithms offering alternatives to least squares curve-fitting have been developed on a trial basis.

Ongoing mathematical modeling of the passive integrative behavior of single neurons has considered the transient response to individual synaptic inputs at single branches in the dendritic tree. This work, now in manuscript, has been presented at the American Physiological Society's Colloquium on Membranes, Ions, and Impulses during the 1974 FASEB Meeting. Present research efforts on active nerve conduction continue to exploit a simple FitzHugh-Nagumo equation to study the dynamic stability properties of its traveling pulse solutions and their relation to the stimulus-response characteristics of this model axon.

The activities of the Biomathematics and Statistics Section continued along the lines previously established. Study of statistical distribution theory appropriate for multivariable measurements, and particularly for the multivariate lognormal model, was continued. These studies extend previous studies of size and shape variables and treat covariance properties of the multivariate lognormal distribution. Another line of research is that of population models. Discrete time models were studied, and a graphic "increment" plot is being studied as a practical tool for discrimination among models. These latter studies are undertaken in conjunction with a credited research project of a STRIDE trainee at American University. Several manuscripts using discrete time models in conjunction with computer simulation have been completed along with a manuscript on the lognormal distribution.

Also implemented was a conversational computer system which enables non-programmers to transfer sequential datasets between computer disk storage and private magnetic tapes, while maintaining a directory of the tape contents. It is now in use by personnel of the Laboratory of General and Comparative Biochemistry, NIMH, for scientific manuscript storage and retrieval.

Work continued in mathematical studies related to linear algebra, the theory of graphs and linguistic analysis, and the theory of computability. Several publications resulted from this work.

Collaborative effort continued on an NCI project for computer analysis of histological and cytological bladder cancer pictures. An expandable interactive computer software system has been implemented and is described in the DMB report.

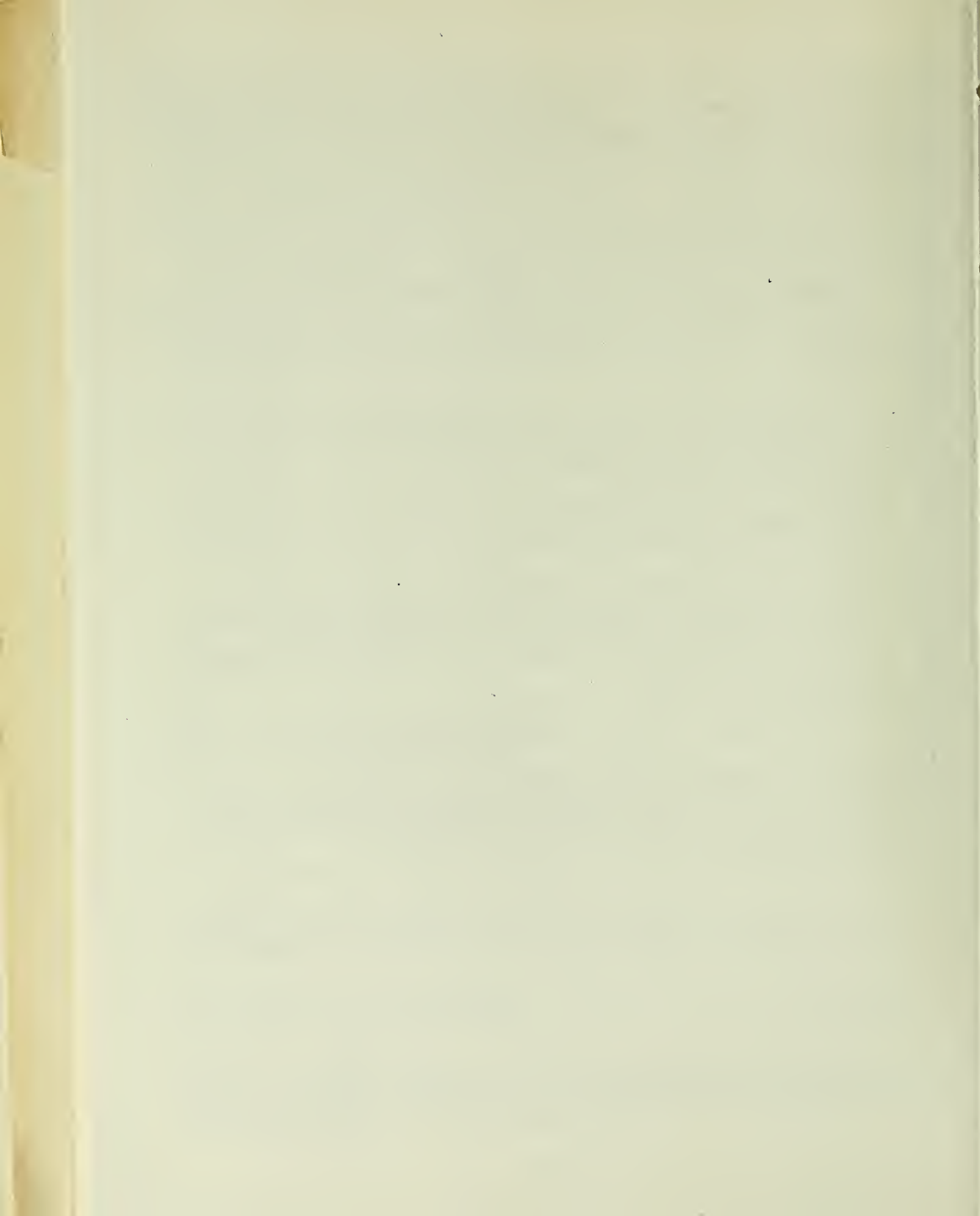
Two members of the laboratory were appointed to an adhoc committee for the Federal Working Group on Pest Management, an interagency group. System models for the transport of DDT and lead through the environment were evaluated.

LAS reports published or "in press" during FY 74:

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*reported as "in press" in FY 73.



Computer Systems Laboratory Annual Report, 1974

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Introduction

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V. Special Consultation

Table of Manpower and Expenditure by Project

Introduction

The primary mission of the Computer Systems Laboratory (CSL) is to identify problem areas in biomedical research and clinical care in which the computer offers a potential for improved research productivity or improved health care. The concentration of work is on applications where real-time data collection, analysis, display, and experiment control are required, where economic considerations favor a small computer or where equipment proximity is important.

The staff of CSL has, in addition to expertise in both the engineering and programming aspects of laboratory computing and automation, extensive experience in working on problems in the biomedical area. Many of the laboratory's projects require a coordinated effort between engineers and computer scientists from CSL and researchers from other Divisions and Institutes.

I. Continuing Computer Support for On-line Laboratory Experimentation

CSL is engaged in a number of projects supporting research in the physical and behavioral sciences. The primary goal of this support is automation of the collection and processing of laboratory data.

This data, which originates in a variety of forms, from a human pushing a button in response to a stimulus to an analytical instrument measuring a physical property of a molecule, must first be converted to a form which can be transmitted to a computer. The CSL engineering staff has developed such interfacing equipment for a number of applications. CSL has developed two laboratory computer systems in NIAID and one in NIAIP which aid research on the structure of complex molecules such as proteins and RNA. The analytical instruments which CSL has interfaced to computers includes spectrophotometers, a nuclear magnetic resonance (NMR) spectrometer, a spectropolarimeter, and an amino acid analyzer, all of which are used to measure different physical properties of molecules. A system developed by CSL for NIMH collects and processes data from human subjects participating in psychological experimentation. The information collected includes physiological measurements and subject responses. The general mode of operation is for a subject to respond to a computer controlled stimulus while the computer evaluates and records the subject's responses, reaction time, and physiological state.

Generally, the smaller laboratory computer systems are devoted to a single user at a time, which is the case with the NMR system in NIAID, where the computer is used for Fourier transform spectroscopy calculations. The NIAIP system, on the other hand, is designed to service a number of experiments in one laboratory at the same time. Here the data are being collected as part of research into the structure of immunologically important proteins. The NIMH and the larger NIAID systems have been developed to communicate simultaneously with a number of laboratories located remote from the computer. During the past year a microspectrophotometer was interfaced to the NIAID computer to make a total of five analytical instruments and two small computers currently on-line. Rather than being interfaced to specific instruments the NIMH system provides general purpose stations which permit the psychological researcher to connect a selection of equipment specific to his

experimental design. Currently eight stations with slightly different configurations are available to the researchers.

II. Two New Laboratory Computer Projects

CSL has undertaken two new laboratory computer projects in the past year, one in support of research on the retina and another involving a new instrument used in cancer research for separating cells.

Laboratory of Vision Research

A research laboratory has been organized in the Laboratory of Vision Research, NCI, for the study of how visual pigments serve to initiate the phototransduction process in the retina and how this process is linked to the transmission of signals from the visual pigment-containing photo-excited region of the cell to its remote pre-synaptic terminal. A variety of physical and chemical experimental methods will be employed and in most cases the data from the experimental laboratory instruments will be in the form of analog voltage signals which vary as a function of time.

A hardwired signal averager and computer have been linked to capture, store and analyze data from these experiments. Presently software is being written which will cause various transfers and manipulations of data to take place. A simple keyboard interrogated by the computer will be used to communicate the functions desired by the researcher when the system is in use in the laboratory.

Fluorescence Activated Cell Separator

Two types of Fluorescence Activated Cell Separators (FACS) are now operational in the NCI. The two systems, which were developed under contract by Stanford University and Los Alamos Scientific Laboratories, have basic similarities. Cells are rendered differentially fluorescent and incorporated into a small liquid stream illuminated by a laser beam. Cells pass sequentially through the beam and the fluorescent light produces electrical signals. Downstream of the laser, the fluid is broken into a series of uniform drops. These drops are charged appropriately and deflected into separate containers. One fluorescence and one light scatter signal are used in the Stanford system to determine cell deflection. The Los Alamos system uses fluorescence at two wavelengths, light scatter and Coulter volume to determine cell deflection. A fluorescence or light scatter distribution is presented using a conventional

pulse height analyzer (PHA) as a means of analysis in both systems. Data collected using the PHA can be formatted to show the distribution of both fluorescence and scatter versus number of cells.

CSI has proposed a small computer system to collect data from FACS on-line and from the Los Alamos system by playback of an analog tape. CSI will interface the instrument to the computer and will develop programs which monitor data collection and process the data. Data entering the computer can either be sent directly out to disk storage for later evaluation, or it can be sorted immediately into a 64 x 64 channel matrix of fluorescence and scatter versus cell counts. This is the same matrix which the PHA is capable of building. However, the computer can sort this data on a specific channel, make comparisons with previously collected data and save results - all of which is not possible with the PHA alone. A display unit will be provided to facilitate the observation, comparison and modification of data distribution. Data analysis will incorporate the normal complement of computational functions such as integration and normalization of curves and statistical evaluation of distributions. The system will be able to produce a hardcopy of displayed results and maintain a permanent file of distributions for further reference.

III. Clinical Care and Research

CSL has, for the last several years, become increasingly involved in the support of many of the clinical care and research functions at the MHI. This has occurred because of increasing understanding and awareness by clinicians of the potential of computers and automation and due to tremendous increases in the amount of data that is analyzed and examined for the diagnosis and treatment of patients. The increase in data has resulted in part from advances in medical instrumentation and techniques which have led to the capability for generating voluminous amounts of data that in turn require sophisticated reduction and analysis to be of any use.

The primary goals in applying automation to clinical medicine are to have computers perform functions which cannot be performed by manual means and to perform routine clerical functions often done by medical personnel so that the talents, training, and experience of these people can be more effectively used.

The projects described here are related to many facets of patient care and clinical research. The technical requirements of all of these projects include the acquisition, storage, analysis, and display of clinical data, and, in most cases, there is a need for these functions to be performed on-line and in real-time. Furthermore, all require extensive cooperation among engineers, computer scientists, programmers, and medical personnel.

MHI Intensive Care Unit

The purpose of this activity is the continuous monitoring of patients in the heart surgery recovery area in order to provide the earliest possible detection of abnormal or dangerous conditions. For over a year now, a computer system has been in operation and performing this function for a single patient by collecting and analyzing ECG, temperature, fluid loss, and arterial and venous pressures. This capability is to be extended so that the same functions can be provided simultaneously for four patients by mid-summer, 1974. Future plans beyond that time include the development of methods for the automatic control of blood and drug infusion, with the control based upon the analysis of monitored clinical signals.

Clinical Pathology Laboratory

In FY73 CSL began an effort to overcome problems of reliability, inadequate flexibility, and insufficient capacity to handle the laboratory workload presented to the existing clinical laboratory computer system. It was immediately apparent that the only realistic long term solution was total replacement of the existing system. However, certain of the problems needed immediate attention before the longer term effort could begin. As a result a new test result entry system was developed for the Chemistry and Hematology service. Test results are now entered via CRT terminals and special devices designed by CSL for the acquisition of data from Coulter automatic blood counters. The terminals and special interfaces are controlled by two minicomputers, one in the Chemistry service and one in Hematology, which are in turn connected to Clinical Pathology's CDC 3200 computer system for on-line data collection. These subsystems have been fully operational since late summer, 1973, providing significant improvements in both performance and reliability over the system that was used previously.

In addition to the above CSL also began, in mid-1974, the automation of some of the routine operations of the Microbiology Service, where it was considered necessary to investigate methods and procedures by which such data should be handled prior to incorporating these functions into a new clinical laboratory system. This work is therefore considered to be of an interim nature. The goal is to permit the entry and storage of test request and result data in files on the 360/370 system such that the data can be later retrieved by inquiries initiated from a typewriter terminal in the microbiology laboratory. The system is now operating with regard to test request data, but is not fully implemented for test results, since automatic means for the translation of result data to machine readable form has not yet been devised.

CSL began efforts toward replacement of the entire system by developing, in cooperation with the Clinical Center, a Request for Proposals (RFP) for a new Clinical Laboratory Information System. There were no commercial systems proposed which could meet the long term requirements and goals of the clinical laboratories; therefore, CSL has undertaken to develop a new Clinical Laboratory Computer System, a project estimated to take about three years and require 15 to 20 man-years of effort. In the mean time, the

Clinical Center has determined that the performance of the existing system has become intolerable, and a commercial system will be obtained for use as a stopgap measure while the CSL development effort is in progress.

Nuclear Medicine Department

CSL has continued to contribute engineering expertise to a joint project with LAS, PCPT and the Nuclear Medicine Department, CC to more fully develop the potential of a computer system which has been operational for almost two years. The scientific objectives and accomplishments of this project are described in the LAS report. In particular, CSL has participated in the development of a technique for studying cardiac performance. This technique permits visualization of the heart cavities through a non-invasive procedure. Both quantitative and qualitative analysis methods are being investigated.

Phonocardiogram Research

For the past two years CSL has collaborated with the Surgical Branch of MML in the development of methods by which characteristics of the phonocardiogram can be used as diagnostic indices of prosthetic heart valve performance. Phonocardiograms are now routinely taken on about six patients per week and analyzed on the hybrid computer. The analysis involves beat-to-beat correlation of the phonocardiogram and a determination of the ratio of the amplitude of the opening sound to that of the closing sound. There is evidence that these factors can be used to detect and identify certain prosthetic heart valve malfunctions.

Pulmonary Physiology Laboratory

During FY74, CSL completed the automation of some of the clinical and research protocols of the Pulmonary Physiology Laboratory, MML. These involved the automation of routine pulmonary function evaluations and of clinical research activities requiring the measurement of respiratory resistance. This effort has been successful in eliminating the need for medical technologists to perform extensive manual calculations and in allowing the laboratory to accommodate a significant increase in workload without a corresponding increase in staff.

IV. General Research

While the bulk of the work in CSL is connected with laboratory automation and clinical care there is considerable effort devoted to other areas of computer research related to biomedical applications. Currently there are two major areas of general research, the use of computer pattern recognition methods in biomedical problems and the development of a medical telecommunications system.

Pattern Recognition Studies

Work continued in applying pattern recognition techniques to study the relationship between the activity and chemical structure of drugs. The main project involved 163 anti-tumor drugs, the chemical structure of which were described mathematically by counting the number of each type of chemical substructural unit it contained. Two drugs which have the same kind of substructural units are considered alike in structure and, assuming that structure relates to activity, they are alike in activity also. The activity of other drugs of related structure can then be predicted from their structure. Preliminary results indicate that the methods hold promise for screening large numbers of drugs which may have anti-tumor activity. The methods are applicable to other structure-activity studies and work is now beginning with other data.

In other related work being done, chemical compounds are characterized by their mass spectra. Methods are being developed to obtain the right combination of masses to describe the compounds in order to improve classification of unknown compounds from their mass spectra.

Medical Telecommunications System

For several years CSL has been engaged in the development of a technology by which computer services can be made available to the medical community using only a conventional touchtone telephone as a computer terminal. The plan has been to make such services readily available so that the power of the computer can be applied in assisting physicians in such areas as diagnosis, treatment, and therapy planning.

A prototype system has been completed which permits the use of the pushbuttons on the telephone as a means of providing input to the computer, while the computer responds in voice over the telephone. A number of medical application programs have also been developed which are indicative of the types of applications which might be used. The medical school of the University of Wisconsin has expressed interest in using the system for a set of applications in the University hospital, and possibly among a group of community physicians. CSL has agreed to collaborate with the University for this purpose. This venture is expected to continue through FY75, after which an evaluation will be made as to the disposition of the project.

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V. Special Consultation

In addition to the work described, CSL consults with researchers in need of computer expertise. This consultation can be simply advice on a specific problem or can result in the design of a piece of special purpose hardware or in the writing of special software.

A typical example of this type of supportive work occurred with a data collection problem arising in NIANPP, for which CSL's advice was sought. An instrument existed which determined the size spectrum of particles and stored that data, in digital form, on a magnetic tape cassette. A CSL engineer modified this equipment and added a communication interface so that digital data can now be sent to the PDP-10 computer, via telephone lines, for further processing. The modifications built for this system have shown the feasibility of this approach and can be adapted to other small laboratory data collection systems to allow them to transmit data for processing on the central facility.

Summary of
LEVEL OF EFFORT AND EXPENDITURE
BY PROJECT

Object Name	Project Leader	<u>DCRT Man-Power (M-Y/Year)</u>		<u>DCRT Capital Invested</u> <u>(\$X1000) including maint.</u>	
		FY-73	FY-74	FY-73	FY-74
Bldg. 2 516	Shapiro	3	2	6K	2K
NMR	Colburn	2	2	20.7K	24.8K
NIMH	Syed	2	2	0	0
NIAID -Waxdal	Shapiro	2	3	5K	9K
NEI	Schultz	1	1.5	0	1K
NCI	Schultz	0	1	0	0
	Syed	7	7	80K	80.6K
Clin. Path.	Plexico	3	4	5K	0
Nuclear Med.	Schultz	.5	.5	5K	40K
Phonocardiogram	Schultz	.5	.5	.5K	.5K
Medical Tele-communications	Plexico	.5	1	14.5K	3K
Pattern Recognition	Shapiro	2	3	0	0
Pulmonary Lab.		2	1	2K	0

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July 1, 1973 through June 30, 1974

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT - 5

2. PHYSICAL SCIENCES LABORATORY

3. Dr. G. H. Weiss

I. OBJECTIVES

The Physical Sciences Laboratory is devoted to the study of problems in physics and chemistry that relate to the biological sciences. Several disciplines are represented in the membership of the laboratory. These include applied mathematics, theoretical chemistry, and theoretical physics. Whenever possible the theoretical studies are performed in conjunction with experimental work, either in collaboration with workers in outside units, or by members of the Physical Sciences Laboratory working in other laboratories at NIH. In addition to performing research of its own choosing, members of the Physical Sciences Laboratory provide consultation to other researchers at NIH on different topics in the disciplines represented in the Laboratory. These services are enumerated in the project reports.

II. CURRENT LABORATORY PROGRAMS

1. Research in the general area of biochemical separation techniques has been carried forth with three objectives in mind: the elucidation of physical and chemical effects that bear on separation techniques; development of methods of processing data from analytical techniques, and development of new methodology in the separation methods. In this past year Dr. George Weiss has, in collaboration with Professor N. Catsimpoolas of M.I.T. and Dr. David Rodbard of NICHD, given a theoretical analysis of transient isoelectric focussing, a separation technique currently in use in the equilibrium regime only. Data from the transient phase can be used to furnish more detailed molecular parameters than has so far been possible. Experimental work on transient isoelectric focussing is being carried out by Professor Catsimpoolas and his collaborators at MIT. Another project in this area is the elucidation of the effects of molecular heterogeneity on resolution in chromatography and electrophoresis. We have shown that heterogeneity sets practical limits on the ability of systems to resolve molecular species. Further work is being carried out in the area of resolution in chromatographic systems. The classical definition of resolution is inadequate for the design of systems with a gradient of properties. We are presently developing alternative methods for specifying the resolving power of a system that can be used for the more general systems now in use, such as two dimensional electrophoresis or pore gradient electrophoresis.

2. Another area of investigation is that of elucidating physical forces in biological entities in order to interpret the phenomenon of biological assembly (cell membrane formation, protein association, cellular aggregation into tissues) in physical terms. Progress during the past year has been in the development of new expressions for interaction energies and the successful design of experimental systems to measure physical forces. The theory of van der Waals forces between large bodies has been developed to include the influence of spatially varying distributions of material at their surface. Drs. Parsegian and Weiss have also succeeded in formulating the attraction between parallel curved spherical and cylindrical bodies. A physical method has been found that facilitates computation of electrostatic forces between rodlike particles, in collaboration with Professor S. Brenner of the University of Kentucky. The results have been applied to the phenomenon of gel formation by Tobacco Mosaic Virus. A successful combination of experimental measurements by Dr. A. Shih at the National Bureau of Standards and theory developed by Dr. Parsegian has been used to analyze the attraction of single atoms or molecules passing in a beam near a solid substrate. This is an extremely sensitive technique for the measurement of forces on the molecular level. A second experimental method, for the measurement of forces between lipid membranes has been developed in collaboration with Professor P. Rand of Brock University, Ontario. It was found that the attraction forces between membranes vary with the presence of solute particles in the water as theoretically predicted by Dr. Parsegian. A method was developed to exert forces on the membranes themselves to measure repulsive forces between them.

3. Techniques of intensity fluctuation spectroscopy for measuring hydrodynamic coefficients of biological macromolecules, swimming speed distributions of motile microorganisms, and the electrophoretic mobilities of blood cells and platelets are being jointly developed by Dr. Ralph Nossal, Professor S.H. Chen of MIT, and Professor B. Berne of Columbia. Recent work on this project concerns the effects of optical heterogeneity on the inelastic light scattering spectra of large particles. The presence of chromatin rich regions within a cell leads to a reduction of the effective size of a microorganism as measured by its light scattering spectrum.

4. Dr. Ralph Nossal in collaboration with Dr. L. Kohn, NIAMDD and Dr. B. Nisula, NICHD have developed refined Leukocyte Migration Inhibition (MIF) tests for detecting tissue antigens. The assay can be adapted to test for cellular autoimmune sensitivity to thyroid tissues of patients having various manifestations of thyroid disease. For example, it has been found that an agranulocytic patient having Graue's disease shows a positive MIF response despite the absence of PMN leukocytes in their peripheral blood.

5. Dr. James Ferretti in collaboration with Dr. E. Becker, NIAMDD, V. Colburn of DCRT, and T. Clem of DRS, has developed a fast scan technique to obtain NMR spectra. Two working NMR spectrometers have been modified to permit spectra to be scanned in very short times (often less than two seconds). The responses are digitized, time averaged, and stored in a Raytheon 704 computer. The computer is then used to crosscorrelate the data either with a suitable reference response or with an analytical function. The rapid scan technique

compares favorably with pulse methods in sensitivity and in some instances has distinct advantages over the pulse techniques. An important advantage is the simplicity of the additional instrumentation required.

6. Dr. George Weiss, together with Dr. D. Hoel, NIEHS, and Dr. R. Simon, NCI have continued development of adaptive sampling techniques to be applied to the design and analysis of clinical trials. Several methods were compared for choosing the better of two treatments in which success is measured in terms of survival time. One technique, suggested by Flehinger and Louis was found to be obviously superior and quite robust. This method was modified to give a stopping rule and adaptive sampling procedure for choosing the better of two dichotomous treatments (i.e., results are given either as success or failure). The resulting technique was found to be considerably more efficient than all others given in the literature. A further application was made to the problem of deciding whether a new treatment is better than a control treatment. Here too, the likelihood method proved to be the method of choice.

7. Drs. Robert Jernigan and James Ferretti are studying the kinetics of the helix-coil transitions of polypeptides in solution. Relaxation times and time correlation functions have been calculated on the basis of a single helical region in the chain, as is usually the case for short polypeptide chains. The calculated values of these parameters can be compared with experimental results to obtain kinetic parameters. The results so obtained are in disagreement with values derived from the current theoretical interpretation, the differences being several orders of magnitude for short chains. Although the newer theory has not been validated experimentally (nor has the older one) it takes into account dependence on chain size, and so might be expected to be more accurate.

8. Dr. James Ferretti, collaborating with Dr. N. Sharpless, NIAMDD, have been measuring NMR spectra at 220 MHz and analyzing the results using the computer program UEAITR written for the PDP-10. In this way they have found that the spin-coupling constants are not simply related to the electron density but that the chemical shift and electron densities are linearly related.

9. Drs. Robert Jernigan and George Weiss have begun a study of the validity of the rotational isomeric approximation for calculating configurational properties of macromolecules. For short chains it is possible to obtain, essentially by enumeration, effects of details of the energy contour on configurational properties. The distribution functions that are being calculated allow one to check various approximations that are presently in wide use. Present results suggest that these approximations may lead to erroneous results. In connection with this project an international symposium was held at NIH in February on Configurational Properties of Biopolymers.

10. In addition to the individual research projects enumerated in the preceding paragraphs, members of the Physical Sciences Laboratory engage in a large number of consulting activities in collaboration with other scientists at NIH as well as in the broader biomedical community. Specifically, Richard Shrager has made extensive use of curve fitting techniques on collaborative

problems. He has applied these techniques to fitting potentiometric and thermometric data for the titration of proteins supplied by Drs. R. Berger, NHLI and M. Marini, Northwestern U.. He has furnished technical assistance on the problem of the digestion of fibrogen by trypsin, with data from Drs. E. Mihalyi and D. Towne, NHLI, as well as on the determination of rate parameters for fumarase kinetics with Dr. L. Kohn, MIAMDD and Dr. I. Darvey, University of Sydney. Mr. Shrager, D. Ashbrook, and G. Knott of DCRT have improved and updated Modelaide and MLAB programs. Modelaide has been revised extensively and now runs on TSO. Mrs. Mildred McNeel has worked extensively with Dr. W. Caveness, NINDS, and Dr. B. Rish, Naval Medical Center, on data relating to head injuries to veterans of the Korean and Vietnam wars, She and Dr. George Weiss have also worked with Dr. E. Fishmann of Freedmen's Hospital on the use of EKG surface maps as a diagnostic aid in left ventricular hypertrophy and acute myocardial infarction. Mrs. McNeel has also helped Drs. Jack Cohen, NICHD and M. Hayes, NIAMDD to compile a review on nuclear magnetic resonance of amino acids, peptides and proteins. Dr. Adrian Parsegian has led a tutorial seminar on The Physical Approach to Cell Membranes and Dr. George Weiss has given a series of lectures on Numerical Analysis for DCRT.

11. Dr. Adrian Parsegian has been elected a member of the Council of the Biophysical Society.

Dr. George Weiss has been appointed a member of the NIH Medical Board.

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July 1, 1973 through June 30, 1974

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT 6
Serial Number
2. HEURISTICS LABORATORY
3. James R. Slagle
Chief

Heuristics Laboratory had a very fruitful year. More than twenty papers are either published or accepted, about three papers per man-year. Most problems undertaken by the staff or the Laboratory are concerned with the application of computers to biomedical fields. Since these problems are large and difficult, efficient and heuristic methods are needed to solve them. Therefore, the activities of the Laboratory are creative and at the frontier of computer application, and are different from those routinely implementing existing methods and systems. The projects worked upon by the Heuristics Laboratory during the fiscal year are summarized as follows: (The names of members of the Laboratory involved in each project are listed in parenthesis.)

A NEW DESIGN FOR CHEMICAL STRUCTURE SEARCH (Modes):

We are collaborating with the Walter Reed Army Institute of Research (WRAIR) on the design of a chemical substructure system in conjunction with the conversion of the obsolete WRAIR system from a second generation to a third generation computer. The new system will allow searching on-line for both structure and substructure, and will accommodate a file whose compounds can number in the millions. There are two basic new elements in our design. First is the establishment of a system of structure fragment screens. We have developed a uniform, iterative method for determining a complete set of screens from single atoms to quite large fragments. Second, is a new use of hash coding, which for the first time brings to bear the full speed of random access on substructure searching. These two elements have been integrated into a rational framework based on new theoretical work on the discrimination power of screens. We have obtained an elegant and practical design whose performance is versatile, predictable and efficient, and an improvement over other chemical search systems. Preliminary results on establishing screening fragments have been gratifying.

MASS SPECTRAL SEARCH (Heller):

As of September 1, 1973 the NIH Mass Spec Search System (MSSS) was officially put on the international GE computer network by the United Kingdom Spec Data Centre. NIH's role in the future will be that of a consultant for the system. A copy of the system remains at NIH for internal use and further research and development.

INTERPRETATION OF MASS SPECTROMETRY DATA (Slagle, Chan, and Heller):

A program was developed to reorganize a large file of mass spectral data. From the display of the reorganized data, we were able to define new groups of compounds by the presences and the absences of certain mass spectral peaks. So far, we have good results for four groups: thiolesters, sulfoxides, aromatic carbamates, and amino esters. The definition rules for these groups have been tested intensively, and found to be able to discriminate a compound in the groups from other compounds not in the groups.

MLAB - AN ON-LINE MODELING LABORATORY (Knott):

MLAB has been further developed. We have spent considerable time promoting MLAB and collaborating with users in setting up models and applying them. The third edition of the MLAB manual has been prepared. Using MLAB jointly with Jean-Marie Ketelslager, we have obtained some results on hormone binding.

MICROBIOLOGY DATA BANK (Norton):

Collaborating with Dr. Krichevsky of NIDR, we revised the program for inputting data to the microbiology data bank to give considerably more extensive diagnostic messages in cases of deviations from the specified input format which it will not forgive.

TISSUE TYPING COMPUTER AIDS (Dixon and Norton):

We are collaborating with Dr. Kayhoe of NIAID on the evaluation of the 1330 trays using the tissue-typing program. The results demonstrated new patterns of serum-antigen specificity on the NIH tray. That is, the program enabled many "false pointers" previously interpreted as "noise" or laboratory error to be interpreted systematically in terms of (sometimes weak) serum reactions to antigens determinants.

COMPUTER MODEL OF THE HUMAN MENSTRUAL CYCLE (Dixon):

We are collaborating with Dr. Cargille of NICHD on the modeling of the human menstrual cycle. A computer model written in the DYNAMO language simulates the process of ovulation and the variation of hormones during the human menstrual cycle. Last year the model did a good job of simulating the normal cycle and a dynamic mechanism for atresia was postulated and put into the model. This year the model was completely rewritten. Many awkward equations were streamlined and the whole model was made simpler and easier to understand. This new version of the model was called MARK4. A simulation of pregnancy was also included in MARK4. A statistical version of the model called MARK5 was also written. MARK5 can be run for many cycles and statistics of hormone levels at various times during the cycle can be collected automatically. MARK6 was also written. This is a version of MARK5 which uses a larger time interval (DT) so long runs can be made at less expense. A set of about 10 validity tests was then prepared. The model passed half the validity tests without change. Modifications were then made to the model to get it to pass the rest of the tests. This work is still in progress.

COMPUTER INFERENCE AND LEARNING (Dixon):

The goal of this project is to develop a program to discover relationships in numerical data. It is hoped that this program will be of practical use to research workers in all fields for automatic analysis of experimental data. The basic idea is to improve the standard technique of linear multiple regression analysis by using products of predictors as if they were new predictors. One might call this technique non-linear regression analysis. Heuristics are necessary to reduce the very large number of possible combinations to a reasonable number. A basic program called ACID2 was written. ACID2 does a multiple regression analysis on a given data set by the stepwise method. All products of predictors are used. The models thus obtained are then tested on a portion of the data not used in the regression analysis. This is called the acid test - hence the name of the program. A number of auxiliary programs have been written to collect, fabricate and manipulate data sets for this program. There are now 10 data sets on which to test this program. They include blood pressure data, tissue typing data, stock market averages, a computer simulated vehicle, a computer simulated radio, tables of random numbers, as well as others. The ACID2 program is in a primitive condition. No heuristics are used at present. It is hoped that the model will be able to learn its own heuristics. But preliminary results indicate that non-linear regression works better than linear regression.

AUTOMATIC PROGRAM-VERIFICATION (Slagle, Chang and Lee):

The application of theorem proving techniques to program verification was considered. A new and direct technique for proving programs correct was obtained. Progress in this field may eventually enable us to test whether software is reliable or not.

AUTOMATIC PATTERN RECOGNITION (Slagle, Chang and Lee):

An algorithm for finding prototypes for a nearest neighbor classifier was developed. The algorithm was applied to 514 cases of liver disease, and only 34 prototypes were found necessary to achieve 100 % of correct diagnosis.

In addition, many clustering algorithms were tested. The short spanning path algorithm was found to be simpler and comparable with the minimum spanning tree method.

PROFESSIONAL ACTIVITIES:

J. R. Slagle participated in the National Institute of Education Planning Conference on Productivity and Efficiency in Education in the United States. He gave a computer science seminar at IBM Research Center at Yorktown Heights, the State University of New York at Albany, and the University of Texas at Austin.

C. L. Chang gave seminars at the Rutgers University, IBM Research Center at Yorktown Heights, and IBM Research Laboratory at San Jose. He taught with Slagle a DCRT course on pattern recognition.

J. K. Dixon taught two DCRT courses on heuristic programming.

S. R. Heller gave a lecture at the NATO ASI on "Computer Representation and Manipulation of Chemical Information" in Holland, and a talk in the CODATA meeting in Freiburg, Germany.

L. Hodes gave a seminar at the University of Maryland.

G. D. Knott taught MLAB and the graphics courses in DCRT. He has written 3 months worth of INTERFACE articles on various topics. Also, he taught the computer science component of the Computers in Clinical Medicine program sponsored by DCRT.

R. C. T. Lee presented a paper at the International Symposium on Computer and Chinese Input/Output Systems at Taipei, Taiwan, and a paper at the Very High Level Languages Symposium at Santa Monica, Calif. He gave seminars at the Temple University, Philadelphia, the Universities of Texas at Austin, Dallas and Arlington, the University of Michigan, and North Carolina State University. He taught a DCRT course on cluster analysis.

L. Norton participated in a government-wide briefing on DBS systems, giving a 1/2 hour talk on his indexing system.

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July 1, 1973 through June 30, 1974

PIIS-NIH

Division of Computer Research and Technology

Summary of Branch Activities

DCRT

Data Management Branch

J. Emmett Ward
Branch Chief

I. SUMMARY

New computer software capabilities had a significant impact on systems developed by the Data Management Branch during fiscal year 1974. Although the new ARMS system was not the most complex system developed in the branch during the fiscal year, it certainly was the one which best demonstrates the advances made over the past year. Virtually every personnel office at the NIH is entering its data at a communications terminal and each of these offices can retrieve information at the same terminal only minutes after a request is entered.

This same approach, using much more complex programming techniques, has been used in developing a retrospective retrieval system for clinical pathology laboratory data. Requests in prior years were held until there was enough volume to justify an expensive computer run. This often meant several weeks of delay in obtaining valuable research information. Now it is possible for a research investigator to enter a request one day and receive the appropriate laboratory data the next. The most significant aspect of the new approach is that the cost of obtaining this information has dropped from approximately \$500.00 to \$20-\$30 per request. During the next fiscal year it is expected that this same technique can be used to interface other clinical data with the laboratory data to render it more useful for analysis by investigators. It should also be pointed out that this methodology facilitates data security for the Office of Clinical and Management systems in the Clinical Center by enabling terminal control over laboratory data users.

In the highly dynamic world of software support, the branch has embarked on an effort which will combine each of its generative systems into a completely integrated data management system. These systems are extremely useful as individual entities, but require several refinements and much more integration to keep pace with the latest facilities available at the DCRT. As part of this effort, the Recursive Macro Actuated Generator (RMAG) is also being completely modified to improve its input and output capabilities.

The Biological Abstracts biweekly BIOSIS service was subscribed to by the DMB this year as a supplement to the existing Chemical Biological Activities Service. Both services are provided free of charge to the NIH community. During this fiscal year we have also negotiated with the NIH library to advertise both services and to provide assistance to prospective users in preparing profiles of search requests. This relationship seems to be working out quite well.

The Harwell mathematical subroutine library was added to the DCRT Mathematical and Statistical Program Library during the year. These subroutines represent several years of programming effort by personnel at England's Atomic Energy Commission and they should add significantly to the flexibility of the DCRT library. A joint effort has also begun with library users to determine what new facilities should be made available and what old programs and subroutines should be eliminated from the existing library. It is planned that better communications terminal facilities will be added during the next fiscal year.

Under the direction of Mrs. Prewitt and with the continued support of the National Bladder Cancer Project, the PEEP/DECIDE/GRAPH general purpose conversational programming system for syntactic and semantic information processing on structured data bases has matured materially and lead to positive research results. This general purpose system is being used to solve the fundamental problem of classifying patients for treatment and tumor type; localization, extent and progression constitute indispensable information for indicating the modality of choice and the scheduling of therapy. Our role is to develop a hitherto unattempted objective and quantitative basis for bladder histopathology, which is currently regarded as the "penultimate truth", clinical information, cystoscopy, and exfoliative cytology notwithstanding. The data bases consist of stained clinical biopsy specimens, scanned and digitized at high photometric and spatial resolution and magnification at JPL with several visible wavelengths and white light, and analyzed at DCRT with the PEEP/DECIDE/GRAPH systems.

During the past fiscal year, PEEP has acquired new built-in picture operators for global dynamic thresholding based on several principles; spatial derivatives; Laplacians; fast and ultra-fast Fourier and Hadamard transforms and inverses; sub-picture creation automatically, by explicit sampling and interactively via displays; masking; convolution; connectivity determination; medial axis construction, and shape, size, brightness, integrated density, and orientation descriptions. With these capabilities we have been able to perform picture segmentation optimally in the presence of artifacts and inter-cellular debris, to extract cell nuclei, describe nuclear features quantitatively, and assemble attribute lists for pattern recognition and multi-dimensional scaling purposes. We

plan to process 100-220 cells automatically by June, covering the range of Grades I, II and III papillomas and papillary carcinomas. DECIDE facilitates decision-making and pattern recognition by addition for facilities for defining sub-sets, complexes and syndromes, for statistical decision theory (Bayesian, maximum likelihood, other; linear and quadratic), and for tracking error rates. GRAPH, a new system component, provides soft- and hard-copy two and three dimensional displays of curves, graphs and surfaces. Commands are relativistic; that is, they can be issued from the vantage of the viewer or the viewed. Several publications and public addresses on the system and its results for bladder cancer histopathology have been issued.

During the coming fiscal year, we plan to unify the three subsystems, PEEP/DECIDE/GRAPH, into one system on the PDP-10 dual processor. We plan to process and scale or classify cells and tissues in several dozen scans (amounting to several thousand cells). We will attempt to optimize staining by further experimentation with Harris hematoxylin, Feulgen, and galloxyanin-chromalum, and to optimize multispectral scanning wavelengths for resolution of contrast and characterizing morphological detail.

In a highly developmental effort the Data Management Branch is collaborating with Dr. Dinesh Sharma, NHLI, to facilitate the planning and forecasting mechanisms within the OD, NHLI. The basic objectives of this system are to support both strategic and operational planning, to assist in the budget staging and monitoring process, to develop future projections based on past trends and to provide a better method for evaluating manpower and other resource allocations.

The methodology for establishing such a facility will be to combine much of the existing NIH grants, financial and budgeting data with information endemic to the NHLI and to provide this information in summary fashion to the Office of the Director. Facilities such as a flexible terminal based interactive system will be made available to enable quick modification and retrieval of data in formats dictated by the user at the time of access. We have high hopes that, through the efforts of Dr. Sharma and the programming expertise of DMB personnel, the system will be highly useful to the NHLI.

The following is a summary of those systems which were developed by the various sections in the branch and, where appropriate, an abstract of those projects which demand a more detailed explanation. These projects can be summarized best by organization structure.

Documentation and Systems Support Section

1. Clinical Center Data Processing Support

Provided reports to Clinical Center investigators from the Laboratory Data Files (BETA) at their request and according to their specifications.

2. Case 1973 Reports

These annual fiscal year reports will contain 135 different listings, tabulations and ranking tables to be published in five volumes by the OD/ADPPE/ORA. For Fiscal Year 1972 we began to standardize the approach to producing output tables. We achieved only partial success in that 1/3 of the 120 case reports were produced without programming. By using these program generation techniques it is expected that we will avoid reprogramming in several new areas this year. Eventually it is hoped that program generation will significantly reduce the time and resources necessary to support this annual requirement.

3. Trends in Graduate Enrollment and Ph.D. Output in Selected Science and Health Professional Fields. (1962-1963 thru 1970-1971).

4. Redesign of ARMS Personnel System

All institutes without appointing authority are currently using a new terminal based personnel data collection and reporting system. The new system is being integrated with the departmental Terminal Data Collection System and it is anticipated that all of the personnel offices at NIH will have the full power of the new ARMS facility by the end of FY 1974.

5. Vitamin C Study, C.C.

Additional relationship tables were provided at the request of Dr. Chalmers, the former Clinical Center Director.

6. Clinical Center Census Reports

Institute, Ward and Bed complements were changed effective 10/01/73 and the system was modified to reflect these changes. An additional program has been written to provide a recurring monthly Geographic report.

7. Diagnostic Radiology Department Case File, C.C.

This computer system was developed to replace a manual radiology record keeping system. Neither the old manual nor the new automated system records diagnostic information, but provision for doing so is possible.

8. Physician Authority List System, C.C.

Additional programs were written during the year to provide Index cards of physicians involved in patient care. These programs are capable of terminal communication.

9. Fogarty International Center

Data on Russian Scientists, Doctors and Institutions was collected by Library of Congress personnel using prompt programs written by DMB. A "Directory of Institutions" and a "Directory of Personnel" has been produced from this data.

10. NHLI Information System Phase II

System established for collecting, editing and updating of all NHLI extramural programs using data from both the Division of Research Grants (DRG) and the NHLI.

11. Study of Baltimore Cancer Research Center (BCRC) Time Sharing Requirements

At the request of BCRC, the Data Management Branch conducted a study of the possible alternatives to BCRC's present use of Tymshare's computer system. A GSA requirement precludes BCRC's use of the Tymshare service after October, 1974. Results of the study indicate that some use of the Tymshare computer system is necessary until a table making facility can be duplicated either in-house or by another time sharing service. It is anticipated however that Cal-a-Computer will provide much of the new time-sharing support for BCRC and that two of the larger systems, namely Census and Microbiology, will be supported on the DCRT computer system. Work is in process now to accomplish this.

12. NCI Contractor Data System

An automated NCI contractor data base was created using data from the DRG Impac system supplemented by additional elements entered by the NCI. The Research Contracts Branch now has a facility for automatic reporting of both open and pending contract information.

13. NCI/DMB Contract Involvement

Personnel of the section are acting as consultants to various NCI personnel and contractors. These include contracts with Tracor/Jitco, JRB Associates and TRW.

14. Opportunity Skills System, ODA, P

15. Results of Questionnaire on Housing, Transportation and Child Care Needs of NIH Personnel, ODA, P
16. Case 1973 Data Preparation for NSF, OD/ORR
17. NICHD Grants System
18. Blood Assay Test Results, NIMH
19. Lupus Data, NIAMD
20. Computer-assisted Electron Microscopy, NHLI
21. KWIC Indexes for the NIH Central Library, DRS/L

Applied Systems Programming Section

1. Type II Intervention Study.

The system supplies all of the data storage, validation, purification, monitoring, and reporting capabilities required in support of the Type II Intervention Study being conducted by the Lipid Metabolism Branch, NHLI. The reporting capabilities were added this year and the DMB is maintaining the present system. Analysis of the data is partially defined and will continue thru FY 75.

This system makes it possible for Lipid Metabolism Branch personnel to store and to subsequently do reporting and analyses on their patients with blood lipid disorders and to relate these analyses to other family members. It also provides them with listings used as an aid to the doctors for patient handling in the clinic. Of particular current interest is the development of reporting capabilities to serve the Patient Safety Monitoring Committee. Support for the system and training of NHLI personnel in its use is supplied by the DMB.

2. Carcinogenesis Bioassay Data System

This computerized data processing system makes it possible for the Office of the Associate Scientific Director for Carcinogenesis, NCI to control the data acquisition, input, purification, reporting and analysis of animal research data related to the study and identification of various agents in order to determine their carcinogenic effect or capacity. The Study includes many thousands of animals being tested under various contracts awarded by the NCI. Examples of output are a summary report, pathology report, survival curve graph, and weight curve graph. Output can be produced in hard copy or on Micro-fiche for all, selected contracts, or selected experiments in a study. The contractors can, upon request, be provided with a complete data base subset of their data. In addition, the Branch supplies assistance to contractors before and after their studies are included in the system.

The major data management system developmental effort has subsided, however, the DMB continues its support. The attention has now shifted to the analysis phase and the DMB is actively involved in this.

3. Autopsy Data System.

This system makes it possible for Dr. Young of the Comparative Pathology Section, Division of Cancer Treatment, NCI to store and maintain his data and to subsequently do logical retrieval from a data base consisting of the extremely variable Clinical and Pathological diagnosis data in autopsies of cancer patients. The primary purpose of this study is to determine what, if any, relationships exist between the use of specific agents and the occurrence of designated lesions. The computer assistance provided by the DMB includes CPS data acquisition, automatic SNOB encoding of clinical and pathological diagnosis, error correction, edit/update, a fixed format report, and a completely generated COBOL retrieval program executed via TSO, which provides almost complete flexibility in composing quick queries.

4. Computerized Distribution List.

This system will provide the Grant and Contract Guide Distribution Center, DRG, with the capability to create, maintain, and selectively produce labels to be used in the distribution of the Grant and Contract Guide and/or any of the various supplements. The data base will eventually be augmented to include other NIH mailing list requirements.

5. NIH Appropriations and Obligations Information System.

This computerized data processing system provides the Office of Legislative Analysis, OD, NIH, with the facility to maintain a data base of NIH Appropriations and Obligations by total NIH, total NIH minus programs transferred out, by activity within NIH and by activity within program.

6. NIH Personnel Accident Reporting System.

This system utilizes the computer to monitor and retain a complete history of NIH employee accidents, follow-up-actions, and corrective measures taken. It communicates with the DHEW computer system via magnetic tape.

7. NIH Space Management System.

The Space Management System helps the Space Management Office manage NIH space utilization and allocation. It also assists other offices by maintaining information relating to areas containing biological or radiation hazards.

8. Medical Records Discharge Diagnosis System.

The system provides the Clinical Center Medical Records Department with the ability to maintain a current, accurate data file of all Clinical Center in-patients' discharge diagnoses. It also supplies various useful reports and listings in the form of indexed MICROFICHE.

9. NIH International Activities and Personnel Monitoring System for the Fogarty International Center.

10. Type V Intervention Study.

This system provides Dr. Greenberg of the Lipid Metabolism Branch, NHLI with the capability of storing and purifying for analysis data collected by NHLI on patients with TYPE V lipid disorders and their first degree relatives.

11. NIH Central Registry of Biological Agents and Materials.

This system is designed to aid the Environmental Services Branch, DRS, in its administration of the Registry. The primary purpose of the Registry is to make feasible the monitoring of hazardous and potentially hazardous materials and agents in use at NIH.

12. Pharmacy Computer File System.

The Clinical Center Pharmacy maintains a complete, accurate file of relevant information on all drug products which it has available. From this file we produce a variety of reports of use to the Pharmacy itself and to doctors and nurses who prescribe and use Pharmacy drug products. At the same time, the file serves as a centralized, computer readable file of drug information about drugs used in the Clinical Center.

13. Dental Clinic Report.

This is a very basic system that aids the Clinical Investigations and Research Services Branch, NIDR, in maintaining a computerized data base which reflects all dental services rendered by this Branch for all Institutes.

14. Egyptian Autopsy Data Analysis.

Dr. Cheever of the Laboratory of Parasitic Diseases, NIAID, performed approximately 250 autopsies on subjects in Egypt. He now wishes to computerize the data in order that an analysis can be made relating to a specific parasite/parasite egg resident in various organs of the subject's bodies.

15. HL-A Data Maintenance System.

The nature of Dr. Rogentine's study for the Immunology Branch of NCI is to try to determine if there is any connection between specific HL-A types and disease. Now that the system is operational, our role is supportive.

16. DCRT Personnel and Training System.

17. Leukocyte Infusion Update and Reporting System.

The system collects data and reports on Leukocyte Infusion information for the Medicine Branch's Leukemia Service in NCI. The information collected includes specific infusion information, laboratory follow-up information, and infusion series summary information. Data is extracted from two related systems, the Cell Collection and the Donor Recipient Information System. These data are then combined with the Leukocyte Information for other reports.

18. Lipid Protein Study - Lipid Metabolism Branch, NHLI

19. Hypertension Study Data Processing System.

The purpose of the study is to try to find correlations between hypertension and other variables such as the kidney's secretion of different levels of Renin. This effort supports the Reproduction Research Branch, NICHD.

20. Clin/Path Test Result Extraction for the Immunology Branch, NCI

21. EVIF Medical Records Information System.

The Emergency Virus Isolation Facility, NCI, has requested that its data collection and reporting system be made conversational. The effort essentially is a redesign of the existing system to provide total data control within the confines of the Building 41 facility. It is hoped that when the system is completely operational, the loss risk relating to sensitive employee data will virtually be eliminated.

22. Animals for Research.

At the request of the NCI, DMB is developing a completely automated system for the Institute of Laboratory Animal Resources, (ILAR). The intent of the system is to improve the publishing and referencing facilities available from ILAR, which publishes data relating to sources of animal stocks, fluids, tissues and organs.

23. Cigarette Condensate Study System.

The study being conducted by the Etiology Branch, NCI and executed by Hazelton Laboratories is an attempt to determine the possible alternatives for people who must smoke and to establish pathways of minimum risk. DMB provided programming support for the data collection and reporting segment of the project. Analysis will be handled by NCI personnel.

24. Computerized Grant Supported Literature Index.

At the request of the Program Analysis and Evaluation Branch, NCI, the DMB is providing a computerized capability to 1) create and maintain, 2) index on keyword, and 3) print for publishing the Grant Supported Literature Index.

25. Computerized Patient Menu Labels.

This system will search the Admission file for active in-patients and produce three labels for each. The labels will be placed on each of the 3 segments of the patient's daily menu for identification of the meal selection by patient. This will save the Nutrition Department in the Clinical Center from having to hand prepare approximately 900 labels per day.

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Scientific Application Section.

1. Psychophysiological Measures

In support of the Laboratory of Socio and Environmental Studies, NIMH, the Data Management Branch has developed a generalized data management and statistical analysis system for psychological and physiological measurers. During this fiscal year, an artifact detection and removal module for heart rate data was developed, the system was completely documented and the user/system interface using live data was started.

Future efforts will concentrate on the integration of laboratory processing data with the computer and on the possible development of a file maintenance capability.

2. Data Base for Surgery Branch

The Surgery Branch of the NCI had a need for a data collection and reporting system. This included the editing, storing and retrieving of all data related to research projects of the Surgery Branch, NCI.

During the past year two new protocols were incorporated into the system. To date, the DMB has provided CPS data collection/edit prompt programs as well as an update, retrieval and reporting system for nine NCI protocols. Data files have been developed to include one file of common data and an associated auxiliary file. This represents a file of all Surgery Branch Operations including those which have not been expanded into separate protocols. Nine additional protocols for which only core data will be entered are currently being implemented. Analysis of the data may lead to more complete protocols for operations not under special investigation at present.

3. Cancer Survival System NCI

The Survival System was originally developed to support the End Results in Cancer Studies. Maintenance and improvement of the system is the primary goal.

During the year several more requests were made for copies of the system. In addition there has been increased use of the system by elements outside the Cancer End Results Group. A number of minor problems have been solved.

A new submission of cancer data took place this year and the CER personnel ran their own edit and analysis programs with some consultation with us. The next submission of data will involve substantial changes in format, making it necessary to make changes to the Survival System to reflect format and coding changes.

4. Current Awareness Search of Clinical Biological Activities (CBAC)

The biweekly issue of the CBAC data is received from the Chemical Abstracts Service (CAS) in Columbus, Ohio. These issues are used to supply the NIH community with information on current articles related to the chemical-biological area.

Retrospective searches are also run monthly or on demand in special cases.

The major non-routine effort in this area during the year was conversion of all PL/1 programs in the system to the new PL/1 compiler. At the same time, the print program was streamlined in order to realize additional savings.

5. Current Awareness Search of Biological Abstracts (BIOSIS)

This is a new service, offered for the first time at NIH in 1974. Twice a month tapes will be received from the Biological Abstracts Service and information will be disseminated to the NIH Community thru the same vehicle as CBAC.

The major effort went into the development, programming, and testing of the reformat program for this new data base. The original CBAC search program is used for BIOSIS data after reformat.

6. Aortic Valvular Disease

In collaboration with Dr. Walter Henry, NHLI, the DMB is providing programming support for a study which will attempt to define prospective pre-operative risk for heart valve replacement patients.

DMB's main involvement with this project during the past year has been to respond to questions concerning the use of the data collection and file maintenance programs we provided.

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7. Cutting Oil Study

This system supports the efforts of the National Institute of Occupational Safety and Health. It is a study relating job type to mortality and morbidity of cutting oil workers. A data base has been established, and a survival analysis program similar to that developed for the Steelworkers Project will be written.

During the latter half of 1973 a number of frequency tables were produced as a preliminary aid to the development of specifications for the analysis.

8. Federal Women's Program Statistics

The Department of HEW supplies the Federal Women's program with tables reflecting NIH employment and promotions by race, sex, and employment level. Data is extracted from these tables and used to create some graphs. A Calcomp program was set up which allows the production of several different graphs and bar charts as desired. Complete documentation for running the programs was given to Ms. Adele Nusbaum, O, EEO.

9. Gastroenterology Training Review

A coding technique for recording the training, education, and experience information on questionnaires sent out to training grants recipients was devised. After the data was keytaped, frequency counts were computed and sent to Dr. Kitzes, NIAMD.

10. Multiphasic Zone Electrophoresis Programs

The output from these programs (2000 recipes for Gel Electrophoresis Systems) is being distributed thru NTIS. Our only real effort in the past year has been in replacing 3 tapes damaged at NTIS and in supplying JCL procedures to the University of Colorado to enable them to run the retrieval program.

11. Radioimmunoassay Programs

This system of programs which evaluates the Scintillation Counter output of radioimmunoassays is in daily use by NICHD. In collaboration with Dr. Rodbard several revisions have been made to the system to keep pace with changing theory and methodology.

Future plans include the replacement of the plot portion of the system with a new printer plot capability.

12. CBAC/Microfiche Project

The entire CBAC retrospective file was put onto microfiche and the file inverted with respect to keywords, molecular formulae, and CAS registry numbers for Dr. Fales.

During the coming fiscal year we plan to create an on-line disk file on the PDP-10 and to develop a search program which will operate in conjunction with a computer-driven microfiche reader.

13. X-Ray Crystallography

A set of computer programs for implementing direct methods in X-Ray Crystallography was developed at the Medical Foundation of Buffalo. DMB personnel converted, stored and tested these programs for use by Dr. James Silverton, NHLI.

14. Gastroenterology Data Base - Dr. Krueger, NIAMD

This will be a data base of journal abstracts from the literature of Gastroenterology. During fiscal year 1974, reformat and print programs were written. The CBAC system will be utilized for searching the text.

This will be set up on a recurring production basis with a new data tape arriving from the Franklin Institute, Philadelphia, once a month. Volume is expected to be about 3,000 abstracts/year. The researchers in NIAMD will eventually develop and run their own profiles or search requests.

15. Computerize Data from Scintillation Counter

In collaboration with Dr. Stephenson of the Viral Carcinogenesis Branch, NCI, data from a Packard Scintillation Counter is being transmitted over telephone lines from Hazelton Labs in Virginia to the PDP-10 at NIH. Programs for calculating concentrations of proteins being measured by radioimmunoassay and for comparing reactivities of different proteins based on the relative slopes of their titration curves were provided. Currently the option of plotting up to 7 distributions on the same graph is being implemented. Future plans include a test for determining the amount of variation between different assays.

16. Computerize Data from Coulter Counter
Biology, NIAMD. Dr. Shehata, Dr. Kempner

Coulter Counter data is supplied to the PDP-10 via paper tape from the Laboratory of Physical Biology. Dr. Shehata and Dr. Kempner were provided with a program which computes mean, mode, standard deviation, and coefficient of variation for bacteria counts and displays them at the terminal. Future plans include provision of teletype graphs and line-printer graphs. Also being discussed are graphic displays, perhaps using the Omnigraph.

17. Serum Bank - Inventory and Retrieval System

Dr. Alexander, Surgery Branch, NCI has data for about 2500 patients and anticipates up to 10,000 with up to 15 blood samples per patient. An inventory system must be set up to keep track of the freezer location of the serum vials and to store test results for undefined numbers and types of tests on the sera. Also desired are updating and reporting facilities as well as a quick retrieval capability.

Specifications for the system have been developed and implementation has begun.

18. Mass Spectral Search System

During FY 1974, the DMB assumed responsibility for the maintenance of an interactive mass spectral retrieval system. In collaboration with Dr. Fales, Laboratory of Chemistry, NHLI, the DMB revised all programs in the system to accommodate new file formats. A new data file, which increased the number of spectra from 12,000 to 30,000 arrived during the year. This new addition plus interface problems between the system's two computers required expert maintenance support. The dynamic nature of this system will cause many complex problems for the foreseeable future. These problems in turn will require thoughtful and experienced computer support for solution.

19. On-Line Table Creation Facility

At the request of the Chief, DMB, a proposal for an on-line table-creation facility has been written. A system of programs is to be developed to do frequency counts and elementary statistical calculations. It is to be operated in either a time-sharing or batch mode and will permit a user to specify parameters for his job in a problem-oriented notation.

Math/Stat Section

1. Analysis of Data of Inbred Mice and Nutritional Treatments.

In support of DRS programs DMB evaluated data involving rations containing two levels of crude protein and three levels of fat which were fed to four strains of mice. Split plot design and least square analysis programs have been run to evaluate the effects of open formula rations on reproductive performance and reproductive performance with different physical characteristics. Evaluation has also included data on reproductive performance and growth of mice fed rations varying in crude protein and crude fat.

2. Interview Scheduling.

The Clinical Center requested major modifications to the original specifications of the Clinical Associate Interview Scheduling System. Systems modifications to make programs compatible with the new FORTRAN-G1 compiler and I/O packages have also been completed. This system is continuously being updated to take advantage of new computer systems. The original documentation is being modified to reflect new changes in the program and run instructions. The system is used each year around April.

3. Evaluation of CC Heart Data.

The initial objective of providing a massive storage and retrieval capability for chemistry data of the Endocrinology Branch, NHLI has been accomplished. Statistical programs have been prepared to evaluate chemical data combined with patient demographic information and fourier analysis on blood pressure data at 24 hour intervals. The final objective of this study will be to develop a capability to produce recurring statistical output and evaluations that would aid scientists in studying the data.

4. Retrospective Study of Aortic Valve replacement.

A set of programs have been completed to edit data on 700 patients who underwent open heart operations. Simple statistical parameters have also been computed in addition to survival analyses.

5. Lipid Protein Study.

In support of NHLI, this study involves evaluation of data on Type II kindreds whose probands were the first 120 individuals found to have Type II hyperlipoproteinemia at the Clinical Center. To date data description statistics and multivariate variance analyses have been provided. Future plans include the addition of sex and age factors to the analysis.

6. Probit and Logit.

This DBS project involves evaluation of different computational methods in an effort to refine the assessment of biologics products. The programming has undergone major modifications; it computes probits and logits with options to compute individual or pooled slopes, with or without conversion of input data. Additional options in the programs include tests for parallelism and relative potency.

7. Evaluation of Pertussis Potency Tests.

This project involves the evaluation of Pertussis vaccine potency as performed at DBS. Programs performing probit analysis have been extensively utilized in this study. However, additional programming is underway to determine if there are seasonal variations in the test as evidenced by cyclic changes in standard vaccines or changes in the immunity of animals receiving standard vaccines. The findings so far have led to two major innovations in procedure, an increase in the number of animals per dose and careful randomization of mice to vaccines and dose levels.

8. Multiple Family Group Study.

The basic unit of this study is a group therapy session in which several families with disturbed adolescents meet with personnel from the NIMH Adult Psychiatry Branch and the Psychiatric Institute. There have been approximately 100 of these sessions, each session yielding five types of data:

- a. Cohesiveness Questionnaire Data.
- b. "Who-to-Whom" Speech Data.
- c. Ward Value Questionnaire Data.
- d. Sociometry Data.
- e. Seating Position Data.

The first three sets of data have reached the analysis stage. The sociometry data is still in the process of being validated and nothing has been attempted with the seating position data.

9. Type II Intervention Study

This effort is part of the analysis phase of the Type II Study being conducted by the NHLI. In collaboration with Dr. Brensike and the NHLI Biometrics Branch, four PL/1 data retrieval programs, initially begun by user, have been implemented. Upon execution, these programs retrieve data pairs for each patient; eliminating missing or inadmissible data and input these data to a program that computes paired-t tests.

A program has been developed to retrieve and edit different sets of data and to access the SPSS (Statistical Programs for Social Studies) package. One of the features of this package will provide Dr. Brensike with the flexibility to obtain whatever cross-tabulations he wishes.

Future plans include the implementation of the Duncan-Walker probability package for analyzing independent variables.

10. Treatment of Massive Obesity: Changes in Cardiovascular Risk Factors

This study involves analysis of changes in cardiovascular risk factors (i.e. blood pressure, glucose tolerance, blood lipid levels, uric acid, heart size on chest X-ray, electrocardiographic findings) associated with weight loss in patients with massive obesity. One hundred six patients who lost at least one hundred pounds constitute the study population.

The degree of weight loss and the changes in the above risk factors assessed by seventeen parameters measured before and after weight loss are being subjected to systematic analyses in terms of incidence of and degree of abnormality. Changes are correlated with degree of weight loss. Correlations among and between parameters are being derived and analyzed.

11. Carcinogenesis Information Evaluation

The analysis phase of this study involves data from ongoing bioassay experiments in mice. The immediate aim is to detect previously unidentified carcinogens.

A major programming effort has begun on this project. Data for the statistical analysis will be drawn from two files; one, a file containing complete background data for each animal group; the second, a file containing complete individual animal records. Call these the 'Control File' and the 'Individual File' respectively. Initial analysis programs include simple data descriptions, such as counts of animals within a sample and counts of animals with certain pathologies. Survival statistics are also being developed.

12. Radioimmunoassay of GS Antigens

Project involves development of a system to calculate the degree of antigen bound in radioimmunoassay data using one, two or three isotopes. In this procedure the amount of antigen is measured by inhibition of the precipitation of standard labelled antigen and specific antibody. The purpose of the second and third isotopes is to determine non-specific contributions to the precipitate.

Programs have been completed to perform calculations using one and two isotopes and the investigator has received numerous outputs. Programming for three isotopes has just begun.

13. Analysis of Data in Occupational Medicine

Project involves analysis of medical examination data and dynamic ECG records of NASA Headquarters personnel. The initial phase of this project involving regression analysis is complete. No future assistance is planned for this effort.

14. Evaluation of Long Lines models

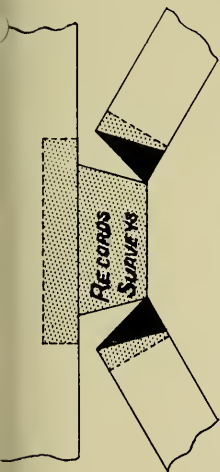
This project involved the conversion and evaluation of three separate systems that compute econometric models used to derive AT&T long lines rates. All of the programs were written by AT&T. DMB's objective in this project was to assist FCC in evaluating these models. The system is now operating on the DCRT computer and has been turned over to FCC personnel.

HOW TO USE
THESE SEPARATORS

Use one page for
each separation.

Select appropriate
tab, add further
identification if
desired, and cover
it with scotch
tape.

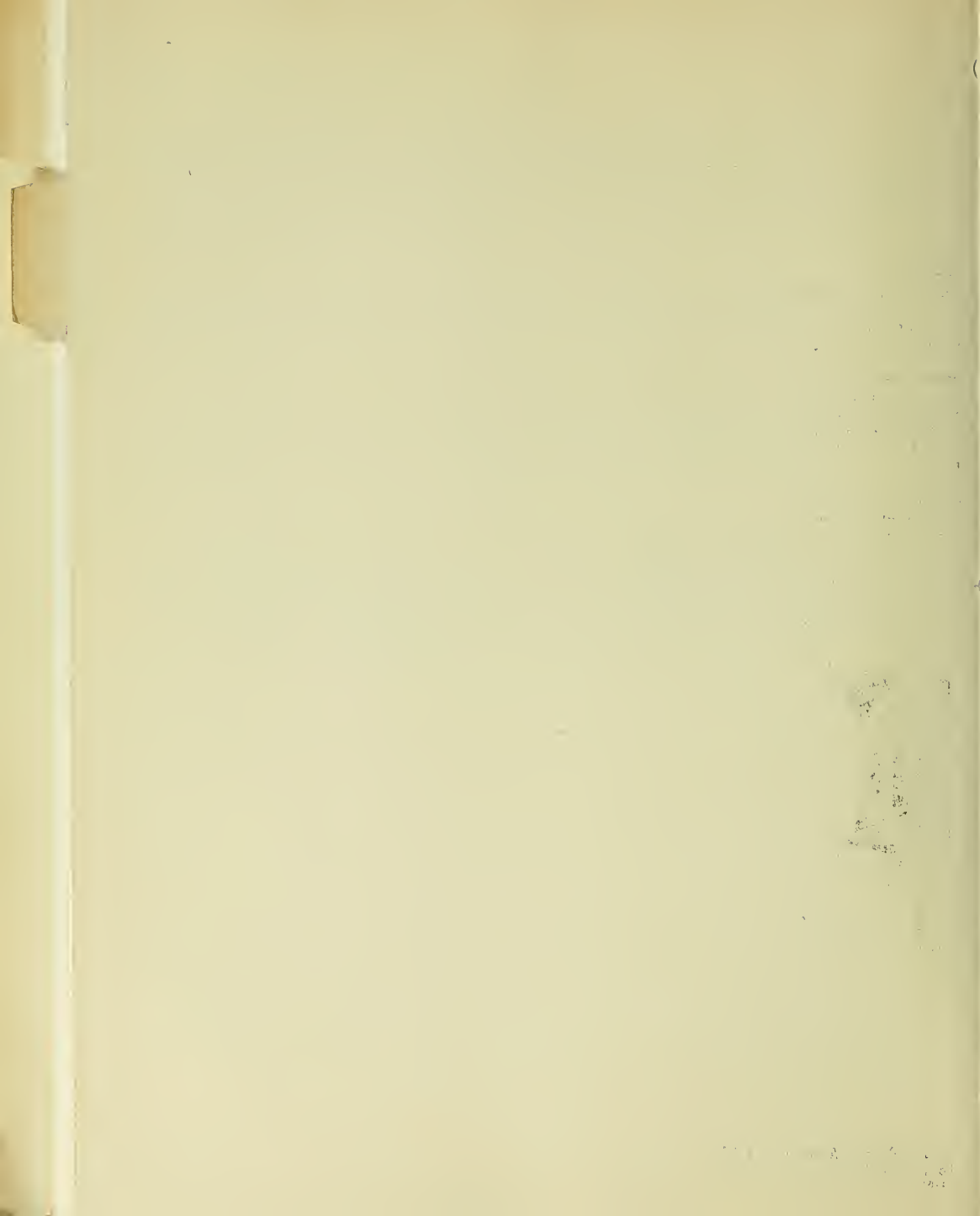
Cut off and discard
all tabs except the
one covered by tape.



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***DIVISION
OF
RESEARCH
GRANTS***

ANNUAL REPORT

Fiscal Year 1974

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HIGHLIGHTS

An unprecedented volume of applications was processed and reviewed-- 25,448, including 2,976 individual research fellowship and research career development awards. Of these, 16,400 competing applications were assigned for technical merit review.

The new research fellowship award program became operative with the February 1, 1974, deadline. Approximately 3,300 individual fellowship applications were received for both the NIH and ADAMHA, and 210 institutional applications.

The Research Career Development Award program was reinstated with June 1, 1974, the initial deadline for receipt of applications.

The number of workshops held by the study sections this fiscal year was five only.

A new computer method for streamlining the monitoring of scientific evaluation grant expenditures has been in operation since July 1973.

Much interest was generated by the report on the project, "Support of Principal Investigators by the NIH: 1966 to 1973," published in *Science*, July 20, 1973. The project and similar studies are therefore continuing.

Classification codes for research contracts were devised to assist in the effort to estimate NIH support of applied research projects and development projects.

A low-cost system of automatically retrieving Notices of Research Projects from a computer tape was devised to provide substantive information about the content of research proposals.

Estimates of available minority and women manpower in the sub-specialties of internal medicine were prepared and documented for a coordinated NIH response to a request from the Department of Internal Medicine, Yale University addressed to all NIH institutes.

A new system for the preparation of the Research Grants Index was completed and the publication was printed by means of the GPO Linotron process utilizing magnetic tapes.

Twenty grantee institutions received audit visits from DRG staff to determine the adequacy with which grantee and contractor institutions are carrying out their responsibilities within the terms of the DHEW policy on protection of human subjects and to initiate negotiations for revision of written assurances to reflect improved performances by these institutions in the protection of human subjects.

New or revised assurances of compliance with the new DHEW policy on the use of warm-blooded animals in research were negotiated with over 600 institutions.

DRG continues to assist DHEW in the application of policy requirements to specific programs and projects involving animals.

A computerized data base of the Report of Expenditures for Fiscal Year 1973 NIH research grants was established.

The establishment of central control offices in grantee institutions for the distribution of grant application kits became operative in January 1974.

OFFICE OF THE DIRECTOR

The Director was present at several scientific meetings during the year under review.

Among the meetings in which he participated were the Council of Graduate Schools Workshop for New Deans held in Seattle, Washington, July 22-27, 1973, at which he spoke on the "Washington Climate"; a Workshop-Conference on Grantsmanship held at Purdue University, Purdue, Indiana, on September 11, 1973, at which he spoke on "Preparing Formal Proposals"; the annual meeting of the Association of Independent Research Institutes held at Bar Harbor, Maine, on October 4-5, 1973, at which he spoke on "News in the Grants Area"; a workshop at the University of Oklahoma, Oklahoma City, Oklahoma, on November 13-14, 1973, at which he spoke on the "NIH Granting Mechanism-Overview"; and a symposium at the Health Science Center at Dallas, University of Texas, Dallas, on March 11, 1974, at which he spoke on "The Grant and Award Mechanisms."

The Director also attended the annual meetings of the Council of Graduate Schools in Williamsburg, Va., on December 12-14, 1973; the Western Association of Graduate Schools in Victoria, B.C., on March 3-5, 1974; the Midwestern Association of Graduate Schools in Chicago, Illinois, on March 24-26, 1974, and the AAMG Northeastern Business Officers Meeting in Philadelphia, Pa., on May 29-31, 1974.

On January 16, 1974, the Director was host to a group of officials from the Instituto Nacional de Investigaciones Agrarias (I.N.I.A.), Madrid, Spain, who were visiting the United States under the sponsorship of the U.S. Department of Agriculture, and representatives of the research agencies of USDA and the Land-Grant universities. Presentations were given by the Director and senior DRG staff members on the mission of the National Institutes of Health, the functions of the Division of Research Grants, and the NIH dual review system for evaluating research proposals.

The Deputy Director spoke at the Biomedical Research Manpower Conference held at the Battelle Seattle Research Center, Seattle, Washington, October 1-3, 1973. He also participated in the NIH Senior Staff Seminar on Management by Objectives, held at Belmont, Md., September 17-19, 1973; the session entitled, "1973 Continuing Education Program," held by the Group on Business Affairs of the Association of American Medical Colleges, New Orleans, La., September 19-21, 1973; the Annual Meeting of the Association of American Medical Colleges, Washington, D.C., November 6-10, 1973; a seminar entitled, "Executive Development Days," held at the National 4-H Foundation Center, Chevy Chase, Md., December 3-4, 1973; the ECEA Seminar on Peer Review, held in Reston, Va., February 26-27, 1974, and the Fourth Advanced Leadership Laboratory for FEI Executives in Ojai, California, June 16-21, 1974.

The Deputy Director is a member of the NIH Executive Committee for Extramural Affairs; the ECEA Subcommittee on Training; the NIH Public Advisory System Coordinating Committee; the Working Group on Projects: Recommendation 2 of the NIH Program Mechanisms Committee Report (Cooper Report); the Study Group on the Protection of Human Subjects in Biomedical and Behavioral Research, and Chairman of the Subgroup on Safeguarding Sensitive Statistical Data.

The Deputy Director organized three DRG staff seminars during the year under review: On July 16, 1973, Mr. Louis Voegler, acting chief, Executive and Management Development Branch, spoke on "Executive Development at NIH"; on October 2, 1973, Dr. Albert Pawlowski, chief, Extramural Research Branch, National Institute on Alcohol Abuse and Alcoholism, ADAMHA, spoke on the "Alcoholism Research Program of the National Institute on Alcohol Abuse and Alcoholism," and on February 22, 1974, Dr. Theodore Cooper, then director NHLI, spoke on "Recent Developments in NHLI."

The Deputy Director authored with the Chief, Research Analysis and Evaluation Branch, a report entitled, "Support of New Principal Investigators by NIH: 1966 to 1972," published in Science, Vol. 181, pp. 241-244, July 20, 1973.

A member of the OD staff has been serving on the NIH Grants Management Advisory Committee and its Operations Sub-Committee; the Program-Project and Center Task Force; the ADERT Unfunded Applications Committee, and as NIH Alternate on the Interagency Standard Application Task Force.

Several staff members continue to work with the Office of the Associate Director for Extramural Research and Training, NIH, in preparing materials for use in the grants program, for example, revising instructions to adapt current application forms to new policies or revising forms to conform with new policies; and developing manual issuances to implement new PHS policies.

On May 15, 1974, a reorganization of the Research Grants Review Branch was put into effect to enable the Division to effectively handle a material increase in DRG's responsibilities for processing and reviewing applications for grants and awards for research and training.

The reorganization abolished the Research Grants Review Branch and established two new branches: (1) the Scientific Review Branch, with responsibility for day-to-day management of review and evaluation activities, and (2) the Referral Branch, with responsibility for day-to-day activities involving receipt, assignment, and processing of all centrally received applications.

The Division's formal employee training program continues to cover both short-term needs and long-range career plans. Fourteen employees are attending Federal City College under the Upward Mobility Program; 16 employees have attended or are planning to attend the Staff Training Extramural Program (STEP); one employee was accepted as an NIH Management Intern, and two employees are participating in the STRIDE Program. Other training included participation in the Employee Executive Training and the NIH Development of Potential Executives Program.

Of the 598 training courses requested during the year, 334 were approved, 260 were completed, 21 are in progress, and 43 are pending. The slight downward trend from last year reflects the lower DRG employment ceiling for this fiscal year.

Members of the Opportunity Program (TOP) Committee formed part of an ad hoc committee appointed by the Director to review and prepare comments and recommendations on proposed revisions of both the Division and NIH Merit

Promotion Plans.

Committee members also attended NIH EEO Council meetings and a seminar held by the NIH EEO Office for supervisors and EEO functionaries, and at the request of the Division's Equal Employment Opportunity Counselor, TOP submitted recommendations for inclusion in a DRG Equal Opportunity Report to employees.

Two members of the Committee were invited by the Employee Relations and Recognition Branch, OPM, to speak to employees on transportation, housing, employee insurance, and other topics of interest.

Most members of the Committee attended a 2-day orientation program held by members of the DRG Personnel Office on the functions of the Personnel Office as they relate to employees and to management.

A film showing, "Prejudice," was sponsored by the Committee for Westwood employees in the belief that films such as this help to stimulate an awareness of prejudices and how to cope with them.

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GRANTS ASSOCIATES PROGRAM

The Grants Associates Program is completing its 12th year as a source of new scientific administrative talent for the National Institutes of Health. Fiscal Year 1974 has been a year of self-examination and evaluation for the Program.

In Fiscal Year 1974 the Grants Associates Board began discussions on ways in which the Program could be strengthened and made more relevant to the present, and possible future, extramural environment of the NIH. A need for better utilization of B/1/D Coordinators was recognized and as a result a plan was developed and submitted to the Associate Director for Extramural Research and Training for comment. In the same vein a "Contingency Plan" was formulated, and approved by ADERT, for the placement of GA graduates during periods of economic stress. A general planning committee has been formed to make an assessment of the extramural activities of the NIH, both grants and contracts, and to make recommendations to the Board as to how the Program can best serve the extramural needs of the B/1/Ds.

An advertisement concerning the Program was placed in the February 15, 1974, issue of Science magazine. Nearly 400 inquiries were received within 60 days as a direct result. Also, the Executive Secretary attended the Federation of American Societies of Experimental Biology meetings in Atlantic City, N.J., in April to recruit for the Program. Forty-four people were interviewed, 14 of whom were given application kits. Approximately 100 job seekers asked to discuss the possibilities of employment at the NIH. The National Institute of General Medical Sciences was assisted in its quest for employees by making the resumé's of those seeking positions available to them.

By April 30, 1974, the Grants Associates Program had processed 516 inquiries regarding the Program. Two hundred and thirty-two applications were received, part of which went directly to the Civil Service Commission for processing. Twenty-seven applicants were reviewed by the Grants Associates Board. Eight accepted invitations to join the Program. Later, for various reasons, two of these had to decline the appointment.

GRANTS INQUIRIES SECTION

The name of the DRG Information Section was officially changed to the DRG Grants Inquiries Section (December 18, 1973), with the approval of the Director, NIH, and in compliance with the Secretary's directive to reorganize the public affairs function into a central organization in each bureau of the Department.

As a service component of the former NIH information organization, the functions of the Grants Inquiries Section were not compatible with those functions established for public affairs personnel. This was the major reason for management's decision to make the Section a non-public affairs component.

The reorganization and subsequent reduction in the number of public affairs personnel also led to a reduction in the number of internal and external periodicals and newsletters. The Division of Research Grants was ordered to cease publication of the NIH/DRG Newsletter, a monthly publication designed to keep grantees informed on changes in policy, procedure, and management, and also the DRG Personnel Items, a monthly publication distributed internally to keep DRG staff informed.

When application control centers were established January 1, 1974, the supply and control of application forms for research project support was transferred from the NIH to its grantee institutions. The Grants Inquiries Section was designated as the responsible NIH unit for maintaining and updating the listing of central control offices in the grantee institutions and for supplying the offices with the appropriate forms (398 and 2006-1).

In March 1974, the Director designated the Grants Inquiries Section as the responsible DRG unit for mailing and billing inquirers for fees involved in searching, reproducing, certifying, and forwarding the materials requested under the provisions of the Freedom of Information Act.

OFFICE OF RESEARCH MANPOWER

At the beginning of FY 1974, the Office of Research Manpower was engaged in operations involving the phaseout of the NIH training programs. During that year all three programs (training grants, fellowships, and research career development awards) were reinstated as a result of the release of Fiscal Year 1973 impounded training funds, but no new applications were accepted in these programs. In addition, two training programs were initiated under the direction of Secretary Weinberger in a new DHEW research manpower program. Also, as a result of the transfer of the Research Career Development Program to research grant funding, applications were solicited for submission by June 1, 1974. In all of these areas, the Office of Research Manpower has been directly involved in developing program policy and announcements, modifying and preparing applications materials, providing information and application kits, contacting previous applicants, and processing applications for these programs.

The details of the new DHEW research manpower program were released in November 1973. Approximately \$30 million was made available for Fiscal Year 1974 to the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) to support two programs, the Individual Research Fellowship and the Institutional Research Fellowship Awards.

The first deadline for these two programs was January 15, 1974, but this was later extended to February 1, 1974. Approximately 3,300 applications were received for both the NIH and ADAMHA under the Individual Research Fellowship Program and 210 under the Institutional Research Fellowship Program. These figures include applications reactivated from the January 1973 and February 1973 deadlines.

The processing of applications was directed by the Office of Research Manpower. Because of the number of applications and the short time to process them, ORM staff was supplemented by other DRG personnel as well as some institute personnel. When the February 1 deadline was over, the ORM processing personnel were transferred to the Project Control Section, Research Grants Review Branch, DRG. In the future, all training application processing will be handled in that Branch.

Regardless of the resurgence of the training programs, the receipt and processing of all types of applications during the 12-month period from April 1973 through March 1974 declined 29 percent from 11,087 applications to 7,833 applications. The competing applications during this period decreased 35 percent from 5,791 to 3,771. The noncompeting applications decreased 23 percent from 5,296 to 4,062 applications. There was an overall decline in the number of training grant and research career development award applications received of 38 percent (4,937 to 3,069) and 39 percent (1,796 to 1,097) respectively. This was mainly because of the decline in competing applications, although noncompeting applications also declined. There was a decline of 13 percent (4,354 to 3,767) in the number of research fellowship applications received. The decline was smaller because of the 3,000 competing applications received in the February deadline.

Of the total applications received in the Office of Research Manpower, 25 percent (1,941) were directed to the Alcohol, Drug Abuse, and Mental Health Administration.

Now that the programs have been reinstated, one of the immediate concerns of the Office of Research Manpower will be the revision of application and program material. The Chief of the Office is the chairman of a drafting committee for the revision of the fellowship application, NIH 1975-1 (formerly PHS 416-1). The committee is working for a June 1 target date for completion of a revised form. Application forms for the other programs will also be reviewed for possible revision. In addition, the numerous policy booklets and award processing forms will have to be reviewed and reissued in the light of the changes in the programs.

The Chief of the Office chaired a committee to develop a manpower report form to obtain annual information about the NIH research grant and contract supported manpower pool. Early in December forms were sent to principal investigators of NIH research grants requesting them to complete the form at the appropriate time so that this information could be available for assessing the country's biomedical manpower needs. Contractors and grantees will be required to submit these forms annually on the award anniversary dates.

ADMINISTRATIVE BRANCH

The study to streamline the previous method of monitoring the scientific evaluation grant expenditures was completed and a new computer method has been operational since July 1973. A monthly cost analysis is produced for management and evaluation purposes, which provides DRG staff with a detailed cost analysis of each study section and committee on a timely basis. Additional management reports are provided by the computer for purposes of administering these funds.

Following the recommendation of the Reference Room Committee, the Reference Room recently acquired more than 50 new texts covering a wide range of scientific subjects, and significantly increased the number of its new journal subscriptions. In addition, the card catalog is being completely reorganized so that all DRG-owned books, including those scattered in various offices in the Westwood Building, will be classified by subject, author, and title. It is expected that the usefulness of the Reference Room will thereby continue to increase.

The Special Services Section provides clerical and automatic typing assistance for DRG and NIH institute/division staff. Three new automatic typewriters using magnetic tape and magnetic cards are in use in the Section. Use of these machines has enabled personnel to complete more than 2,000 letters, 8,000 mailing labels and 300 Summary Statements. In addition to numerous other small jobs, the Section staff has assisted extensively in other offices. The staff has also given individual typing instruction to DRG employees, excluding Section staff, under the Upward Mobility Program.

The Travel Section provides information and assistance for DRG personnel and outside consultants traveling for the Government. During the past fiscal year, they processed and forwarded for payment approximately 4,000 travel vouchers for consultants who serve on the various study sections. These vouchers total over \$2 million. Another \$250,000 was spent to pay travel costs on approximately 700 vouchers for DRG travelers and other Government employees.

The DRG Mail Room received and processed approximately 25,000 research grant applications; 300 NLM grant applications; and 11 construction grant applications; and a large volume of supporting documents, letters, and publications. In addition, the Mail Room assumed the responsibility for handling training grant and fellowship applications.

The Office Services Section compiled and handled an average of 9,000 grant application kits of all types and mailed 9,500 miscellaneous packages a month during the period under review. The Section also provided planning and assistance in accomplishing several major moves within the Division; acquired and maintained equipment, furniture and supplies, and provided duplicating services for Division personnel.

INSTITUTIONAL RELATIONS BRANCH

The Institutional Relations Branch administers the Department of Health, Education, and Welfare policy on the protection of human subjects and the DHEW policy on animal welfare. Other responsibilities of the Branch include establishment of eligibility to serve as a grantee; establishment of eligibility for waiver of equipment accountability under PL 85-934; negotiation of successor in interest agreements; and liaison with OS-DHEW with regard to responsibilities under Title VI of the Civil Rights Act.

The Branch prepared the NIH/DRG Newsletter until its discontinuance in December 1973. The Branch continues to disseminate information on NIH-supported conferences.

Protection of Human Subjects

The Branch has negotiated general assurances with about 700 institutions as required by DHEW policy on the protection of human subjects. In addition, the Branch has negotiated approximately 1,000 single project special assurances with institutions having few active projects involving human subjects.

The Branch has been the focal point for revision of the present policy. This has involved receiving, collating, and evaluating comments from some 200 private institutions and agencies and redrafting the issuance in the form of final rule-making. It is expected that the regulations will be issued before the end of this fiscal year.

The Branch has acted in an advisory and administrative capacity to the special study group appointed by the Director, NIH, and charged with reviewing and recommending policies and special procedures for the protection of children, prisoners, and the institutionalized mentally infirm in research, development and demonstration activities. The report of this study group was published in draft form in the Federal Register¹ during the fiscal year. Some 500 public comments were received and analyzed, and about 150 controlled correspondence letters were requested by congressmen and senior HEW officials. Presently, the Branch is providing continued staff back-up to the members of the special study committee in their efforts to formulate a Notice of Proposed Rule-Making which is expected to be issued this calendar year.

At the request of the Assistant Secretary of Health, the Branch has prepared a revision of a draft Federal policy applicable to activities involving human subjects supported by all or any Federal agencies. This has involved conferences with representatives of other Federal agencies at the policy-making level, and has aimed at producing uniform Federal administrative practices by the end of 1974.

During this fiscal year, staff members organized and participated in systems audit visits to 20 grantee institutions. These visits are designed to determine the adequacy with which grantee and contractor institutions are carrying out their responsibilities within the terms of the DHEW policy and to initiate negotiations for revision of the written assurances to reflect improved performances by these institutions in the protection of human subjects.

Plans are underway to increase the number of these visits during the balance of this year and in the future.

Tuskegee Syphilis Study

Two members of the staff were detailed for 8 months to the Office of the Assistant Secretary for Health, DHEW, to serve as staff to the Tuskegee Syphilis Study Ad Hoc Advisory Panel.

Welfare of Laboratory Animals

The Branch collaborated with Department of Health, Education and Welfare components in publication of a policy statement on animal welfare, and with the National Institutes of Health on revision of policy and establishment of rules to implement departmental requirements. This policy now applies to all warm-blooded animals used under DHEW supported grants and contracts, and enhances the Branch's ability to carry out its assigned responsibilities.

New or revised assurances of compliance with the new policy have been negotiated with over 600 institutions, essentially all those using animals in research supported by NIH grants. Institutions receiving support from other DHEW components and through contracts are submitting assurances as required. NIH contracts now contain a clause requiring compliance with the policy. The Branch will continue to assist DHEW programs in the application of policy requirements to specific programs and projects.

Citizen's complaints and congressional inquiries concerning several grants have been answered. No grantees or contractors have refused to submit or revise assurances or to answer questions concerning their laboratory animals procedures.

Successor in Interest and Name Change Agreements

During the year, the Branch has written the NIH policy and procedure for the negotiation of "Successor in Interest and Name Change Agreements" pertaining to all grant programs. These agreements are necessitated as a result of legislative or other legal action affecting the status of a grantee institution, such as mergers, divestitures, or other corporate changes.

Three agreements are pending at the present time. When these have been concluded, each institute and(or) division will be notified of action taken.

Institutional Control of Research Grant Application Forms

During the past 3 years, 36 major institutions have participated in a study to consider the recommendation that all renewal and continuation application kits be routed through one control point. Follow-up studies from time-to-time indicated that the project was being well received by administrators and that specific internal benefits were being realized, i.e., lines of communication were established which never existed before, better control of budgetary requests was effected, checks for accuracy and timely submissions

were facilitated.

In view of the willingness of grantees to assume more responsibility in the management of grant programs, the Branch developed the policy and procedures to include all grantees under the system of application control. This was effected on January 1, 1974. In addition, it is expected that NIH will realize considerable savings in the cost of applications since the distribution of kits can be confined to one source in the Division.

Equipment Accountability

The Branch continues to serve as the focal point in NIH for carrying out the provisions of PL 85-934, which consist of determining institutional eligibility under the law for "waiver of equipment accountability."

¹Part II, Volume 38, No.221, November 16, 1973

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RESEARCH ANALYSIS AND EVALUATION BRANCH

The project, "Support of New Principal Investigators by NIH: 1966 to 1972" was completed and published in the July 20, 1973 issue of Science. Requests for reprints (4,000) and the interest in this publication has led to a continuation of the project and similar studies, especially those having to do with flux in the population of principal investigators.

Analyses of NIH approval and award rates and key factors affecting award rates in certain biomedical disciplines were the subject of several briefings for OD-NIH staff. Other analyses of the competing research grant programs focused on budget trends over the past decade. A report charting the survival characteristics of grants in selected research programs has been completed and will be available in the near future.

The Research Analysis and Evaluation Branch contributed to the effort to estimate the NIH support of applied research projects and development projects by devising classification purpose codes for research contracts. Another result of this effort was the identification of contracts which provide support for research resources and others which identify the NIH information dissemination system through the contract mechanism. RAEB continues to code all research contracts according to the GSCS code.

Dr. Julio Cesar, an official of the Mexican Government, spent 3 days studying the DRG's information systems and the operation of the Research Analysis and Evaluation Branch to obtain information that would assist the Mexican biomedical research establishment in their classification and organization of research support programs, especially with respect to record keeping, analyses and evaluation.

The Branch continued furnishing information requested by several inter-agency groups or committees. This year NIH was host for the Spring meeting of the Federal Interagency Chemistry Representatives for which arrangements were made by the RAEB staff. Broad questions, especially those that are scientific discipline oriented or those that concern various issues or problems spanning several or all of the institutes and divisions are typical of those that fall within the purview of the Branch.

A staff member devised a low-cost system of automatically retrieving Notices of Research Projects from a computer tape to provide substantive information about the content of research proposals. Documentation of this kind has been found to be a valuable supplement in various analytical studies. Similarly, the system has proved to be useful to the Research Documentation Section of the Statistics and Analysis Branch, which has similar needs.

In response to a request to all of the NIH institutes from the Department of Internal Medicine, Yale University, the Branch prepared and documented an NIH coordinated response on estimates of available minority and women manpower pools in the sub-specialties of internal medicine.

Other specific non-routine requests for information were as follows:

Acupuncture research
Arctic research (principally adaptation to harsh environment and behavior problems)
Care of animals in biomedical research; response to criticism of experiments described in the scientific literature
Diagnostic nuclear medicine
Identification of projects involving marine mammals
Marine research
Research involving the plant sciences
Support of research in schools of pharmacy
Research grants related to rehabilitation
Research in advanced computer technology
PHS projects (principally having to do with alcoholism, drugs, and driving) related to highway transportation research
Nutrition
Hematology

In compiling the above reports, the Branch made extensive use of the DRG information systems, including CRISP, IMPAC and the GSCS codes.

One senior staff member attended a health-scientist management training course in Atlanta; another attended the STEP module on science and public policy in Reston, and in February the Branch Chief attended the Brookings Institution "Policy Conference for Science Executive" held in Williamsburg, Va. Two staff members are attending the Upward Mobility College, and one received the Ph.D. from Catholic University. Numerous individual training courses were taken by other staff members, especially in the area of computer science techniques.

RESEARCH GRANTS REVIEW BRANCH

During Fiscal Year 1974, the Research Grants Review Branch processed and reviewed an unprecedented volume of applications. In February, March, and April 1974, the Branch received, referred, and reviewed a near-record number of applications for research grants and, in the same period, assigned and reviewed approximately 3,000 applications for fellowships. Competing and non-competing applications processed by the Branch during this fiscal year totaled 25,448, including 2,976 applications for individual fellowships and career development awards and 157 for institutional fellowships. Of the total, about 16,400 were competing applications assigned for technical merit review. Approximately 80 percent of the research applications were assigned to NIH. The Branch provided the initial scientific review for about 90 percent of the NIH competing applications for research grants and for all of the NIH applications for individual fellowships and career development awards.

A table showing the distribution of applications processed in fiscal year 1974 is appended to this report.

February 1, 1974, was the first deadline for two new DHEW research manpower programs: the Individual Research Fellowship and the Institutional Research Fellowship Awards. In the assignment, processing and review, within a short time-frame, of the approximately 3,000 applications received, difficult administrative problems were encountered. Problems involved personnel shortages, overcrowded offices, overloaded equipment and facilities, overtaxed services, and so on. Efforts are being made to deal with these problems before the fall review cycle begins.

In September 1973, a revision of the National Institutes of Health Referral Handbook was issued. It is designed as an internal working guide for the Referral Office, DRG, in the assignment of grant applications to awarding agencies of the Public Health Service.

A report from the Radiation Study Section's April 1972 workshop, "Ultrasonics in Medicine," was published in December: "Ultrasound in Diagnostic Medicine," Radiology, Vol. 109, No.3, pages 737-742, December 1973.

Several articles written by a staff member of the Branch, Dr. Rob S. McGutcheon, have been published in PharmIndex: (1) "Drugs of the autonomic nervous system, Part I--Cholinergic drugs and related blocking agents," PharmIndex 15:11A, 1973; (2) "Drugs of the autonomic nervous system, Part II--Adrenergic drugs and related blocking agents," PharmIndex 15:12A, 1973; (3) "Drugs used in diagnosis," PharmIndex 16:2A, 1974; and (4) "Oral contraceptives," PharmIndex 16:5A, 1974.

Dr. Bernice S. Lipkin presented a paper entitled, "Textured Parameters Related to Nuclear Maturation in the Granulocytic Leukocytic Series," at the Engineering Foundation Conference on Automated Cytology at Asilomar, California, December 2-7, 1973. The paper, co-authored with Lewis E. Lipkin, has been accepted by the Journal of Histochemistry and Cytochemistry, Williams and Wilkins Company, publisher.

Affected by budgetary and personnel limitations, the study sections sponsored only five workshops this year. Study sections conduct workshops and conferences to survey the status of research in their areas, enhance reviewer competence, and stimulate research in neglected areas. Two workshops were held in January 1974, and three in April.

On January 9 and 10, the Endocrinology Study Section conducted a workshop in Silver Spring on "Molecular Processes in Secretory Cells." This workshop was organized to summarize recent advances in molecular biology that might relate to hormonal control of the function in secretory cells. The workshop was organized into six subsections: (1) Cell Membrane; Structure and Function, (2) Biology of Steroid-Hormone Receptors, (3) Protein Synthesis-Transcription, (4) Protein Synthesis-Translation, (5) Protein Kinase: Isolation and Function, and (6) Stimulus Secretion Coupling: Molecular Relationships.

The workshop was of extreme interest to the participants and observers and generated a great deal of discussion on new concepts emerging from this field. The plasma cell membrane was discussed in terms of its components and its tremendous fluidity. The point was well made that the plasma membrane is actually in a dynamic state. Recent studies on intracellular membranes, also presented, concluded that membrane segregation is maintained during communication between cellular compartments. The hormone receptors were discussed in some detail in terms of their physical-chemical characteristics, their nuclear binding sites, and their biology as related to hormone induction of specific new processes. Effects of hormones on gene transcription were noted and new techniques emerging from this field were emphasized. It was evident that future work in this field should be coupled with that of hormone receptors and it should eventually be learned how a hormone receptor directs changes in readout of certain gene elements. Whether the hormone receptor complex affects polymerase activation, polymerase binding to DNA, polymerase initiation of transcription, polymerase propagation of transcription, or RNA chain release chain processing, or chain transport will probably be determined in the next 2 years. The mechanisms relating to translation of messenger RNA were discussed in detail and the new systems available for studying endocrine relationships in terms of specific mRNA were reviewed. The translational assay systems are now of sufficient sensitivity to detect the presence of only a few molecules of mRNA. Major progress is being made towards purification of the regulatory and catalytic subunits of protein kinase. Much work is currently in progress to determine the substrates for phosphorylation during hormone action--a key area on which investigators should focus in the next 2 years. The role of a stimulus secretion coupling and its relation to ions, temperature and pH were reviewed. Mechanisms to explain cellular secretion and export were presented. This is also an exciting area of endocrine research, and methodologies now exist to answer a number of long standing questions.

The other January workshop took place in Bethesda on January 16, 1974, when the Nutrition Study Section and invited speakers reviewed the topic, "Carbohydrates." The influence of dietary carbohydrate on health is receiving considerable attention. This interest is fairly recent and the significance of implications which have been made is not currently known. Refined sugar has been implicated as contributing to the development of cardiovascular disease and hyperlipemia. Preliminary evidence suggests that intakes of fiber

influence the development of diverticulosis and colonic cancer. There is considerable interest in the role of trace elements in carbohydrate metabolism. This workshop considered primarily the metabolic consequences of altered intakes of refined sugar and of fiber. The following topics were discussed: (1) sucrose in health and disease; (2) interrelationships of trace elements and dietary carbohydrates; and (3) the role of complex carbohydrates.

After taking inventory of some of the effects of feeding sucrose or fructose to experimental animals and man, discussion of the first topic was directed to the findings of some investigators that there is a strong correlation between fat intake and sugar intake. In certain patients given sucrose when on a diet high in polyunsaturated fats and low in cholesterol, investigators found no induction of hypertriglyceridemia, but they showed a striking hypertriglyceridemia following sucrose when they were eating a saturated fat, high cholesterol diet. These experiments illustrate the importance of studying not only what effects individual diet constituents have, but how they can interact to produce different results.

Presentation and discussion of the second topic emphasized the role of manganese, zinc, and chromium in carbohydrate metabolism. Manganese is not only involved in the synthesis of mucopolysaccharides, but it has a function in glucose metabolism as well. Manganese-deficient guinea pigs have an impaired glucose tolerance test which can be normalized by manganese supplementation, and manganese was shown to have strong hypoglycemic activity in one diabetic subject. Zinc deficiency also results in deterioration of glucose tolerance in rats, as compared to pair-fed controls. These changes are in part due to a reduced secretion of insulin in response to the glucose load, but, in addition, due to a decreased response of the zinc-deficient rats to insulin, as shown by a slower decline of serum glucose levels after insulin injections. That zinc may be a part of endogenous insulin has been postulated by several investigators, but, if there is such a relationship, it is probably restricted to the storage form of the hormone within the pancreas. Chromium is closely related to the peripheral action of insulin; this element has been shown to potentiate the action of insulin in vivo and in vitro. Consequently, chromium deficiency results in a decreased response of the organism to its own and to exogenous insulin, and in impaired glucose tolerance. It is suspected that the consumption of excessive amounts of sucrose that furnish no appreciable chromium can result in substantial chromium losses, but these effects cannot yet be quantified.

In the third presentation problems relating to definition and analysis of complex carbohydrates were described. Crude fiber has been defined by international agreement of the Association of Official Agricultural Chemists as the portion of food that resists extraction first with sulphuric acid and subsequently with sodium hydroxide. The human alimentary enzymes divide the carbohydrates differently. Man can hydrolyse by his digestive enzymes the vegetable cell contents, carbohydrates, fat and protein; but the structural polysaccharides and lignin present in the cell-wall resist hydrolysis. These remnants have been defined as dietary fiber. This complex group of substances surrounds the starch, fat, and protein of all natural plant foods while digestion occurs in the small intestine; then these remnants are hydrolysed in varying degrees by bacteria in the large bowel. Hypotheses and

evidence as to protection against diseases of the large bowel, diabetes, ischemic heart disease, and gallstones, which relatively high intakes of fiber may afford, were discussed.

On April 16 and 17 in Bethesda, the first spring conference was held. Entitled, "Developmental Human Behavior Genetics," it was sponsored by the Developmental Behavioral Sciences Study Section and the National Institute of Child Health and Human Development. Human behavioral geneticists and developmental behavioral scientists met to discuss methods and strategies for the improvement of research in developmental human behavior genetics. The following subjects were presented and discussed: (1) state of the art in developmental human behavior genetics and implications; (2) genetic mechanisms in human behavior development; (3) quantitative genetic perspectives: implications for human development; (4) gene-environment interaction in human behavioral development; (5) empirical methods in quantitative human behavior genetics; (6) populations for the study of behavior traits; (7) use and misuses of behavior genetics: ethics of civil rights and informed consent; and (8) behavior genetic counseling. Several publications from this conference are planned.

"Immune Reactions in Invertebrates" was the subject of a workshop convened by the Tropical Medicine and Parasitology Study Section on April 17 and 18, 1974, in Bethesda. The workshop explored in depth several of the mechanisms in invertebrate immunity which are real and potential determinants of successful parasite transmission by vectors. Equivalent phenomena were compared in different vectors and reservoirs (insects, ticks, snails) and comparisons made of similar mechanisms operative in vertebrate immunity.

The first session, on the invertebrate gut as a barrier to invading parasites, included the following topics: (1) barrier structures of the gut wall; (2) infectious process of insect pathogenic viruses in arthropod gut; (3) interactions of vector with vertebrate pathogenic viruses; (4) biochemical aspects of virus infection in insect gut wall; (5) parasite penetration of peritrophic membranes in vectors; and (6) evidence of genetical control of invertebrate immunity and its field significance.

A second session, on analysis of invertebrate immunity, examined cellular components and hemolymph components in invertebrate immunity. In the final session on vector destruction of parasites, encapsulation, melanization, and host hormones were discussed. Following these topics, vertebrate and invertebrate immune mechanisms were compared. Information gathered during the workshop is being prepared for publication in book form.

The third spring workshop, sponsored by the Reproductive Biology Study Section and the Center for Population Research, NICHD, was held in Bethesda, April 27 and 28. The uterus is the all important organ for conception and pregnancy. A growing number of applications deal with its physiology. It is involved in sperm transport and probable capacitation in some manner. It is the organ involved in implantation, after which it serves as the "home" for the developing fetus until parturition. The cyclic phenomena of the uterus relate to the physiological and psychological well-being of the human female.

At this "Workshop on the Uterus" presentations and discussion were focused on: (1) the structure of the uterus, including epithelium, stroma, and decidualization; (2) the uterus as a model of hormone action, including physiology of estrogen receptors, receptor structure, carbohydrate metabolism, and synthesis of specific RNA and protein as a result of hormones; (3) the uterus as a muscle, including hormonal control of Ca transport in myometrial sarcoplasmic reticulum and the adenyl cyclase system, and (4) other aspects, including uterine fluid proteins and clinical status of prostaglandins as effectors in the uterus.

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APPENDIX

APPLICATIONS PROCESSED BY REFERRAL OFFICE, RGRB
 Fiscal Year 1974: March 16, 1973 - March 15, 1974

COUNCIL	Nov. 1973	March 1974	June 1974
COMPETING			
Types 1, 2, 3	NIH - 3,324	3,358	3,925
	HSMHA - 713	641	1,230
	FDA - 25	28	26
TOTAL	4,062	4,027	5,181
PL 480	6	3	3
Institutional Fellowships			157
Career Development			51
Individual Fellowships			2,925
Subtotal	4,068	4,030	8,317
NON-COMPETING			
(All 3 PHS components)			
Type 5	3,708	2,199	2,121
Interim-Regular			
& Cross Fiscal	429	251	325
Subtotal	4,137	2,450	2,446
TOTALS			
(All 3 PHS components)			
Competing	4,068	4,030	8,317
Non-Competing	4,137	2,450	2,446
TOTAL	8,205	6,480	10,763
Grand Total for FY 1974 (Competing and Non-Competing)			25,448

May 3, 1974
 RGRB

STATISTICS AND ANALYSIS BRANCH

In Fiscal Year 1974, the Statistics and Analysis Branch placed increased emphasis on the "wholesale" dissemination of information and reports. The practice of providing selected data from the Information for Management Planning Analysis and Coordination (IMPAC) and Computer Retrieval of Information on Scientific Projects (CRISP) Systems on magnetic tapes to BIDs was continued with all but one institute availing themselves of this service. To expand the BIDs' understanding of the Central Data System and permit them to fully utilize the magnetic tapes provided, the Branch increased its efforts toward the orientation of BID personnel by expanding its formal training programs on the IMPAC system. These courses highlight and describe the data content and format of information recorded in the IMPAC system and develop proficiency in the use of the Inquiry and Reporting System. In addition, a system was developed to generate special subsets of information contained in the CRISP files describing the scientific content of research grants and contracts. These tapes can be utilized by the BIDs to meet their individual scientific reporting requirements.

Efforts were continued to respond to requests from institutions for development of their information systems in the grants and contracts programs. By providing such assistance, SAB seeks to interact with these institutions in a manner that will:

1. promote the possibility that reductions in future data-capture workload can be effected through the development of data interchange conventions and systems that will be compatible with the IMPAC and CRISP systems, and
2. improve the data integrity of the DRG information systems through the transmittal of information to, and subsequent feedback from, these institutions.

In line with the Branch's service concept, it continued its attempts to be more responsive to user needs in spite of reduced personnel availability.

The Branch continued its support of the NIH Affirmative Action Plan for Equal Employment Opportunity through an active employee training and development plan. Sixty-nine Branch employees participated in 53 different training courses and seminars. Special training programs in which Branch employees were involved included the Upward Mobility College, the attendant Special Career Development Proposal Workshop, and the STEP Continuing Education Program. The three student trainees recruited under the Federal Junior Fellowship Program in 1973 continued their second year of training. Other special programs in which employees participated included the Consumer Education Course and the Retirement Planning Course.

Significant activities and major accomplishments are discussed below.

1. Office of Systems Planning. The Office of Systems Planning, in collaboration with the other Sections of the Branch, continued its activities for expansion of the NIH extramural central data system and for the design and implementation of new applications. Design of

the manpower reporting system and expansion of the Committee Management Information System were two major areas of involvement. These areas are detailed in the reports of the Data Processing Section and the Special Projects and Services Section. A new computerized system for the preparation of the Research Grants Index Volume II was completed and the publication was printed by means of the GPO Linotron process utilizing magnetic tapes. Additionally, efforts were expended in implementing the new counter-signature system for awards, revamping the assignment system for Fiscal Year 1975 Common Account Numbers by program areas, initiating the centralized mailing of continuation application kits for research programs, introducing a new budget category identifying costs for third-party contracts under consortium grants, incorporating P.L. 480 (Foreign Currency) Programs into the overall information system, and establishing a computer system for reporting contract summaries to the Science Information Exchange. A major project was also initiated by the Section to study the feasibility of establishing a terminal system to be utilized by the BIDs in producing a Notice of Grant Award at their work sites.

2. Data Processing Section. The Data Processing Section is responsible for (1) planning and directing a data processing program for the collection, compilation, interpretation, presentation and publication of statistical data pertaining to the extramural programs of the PHS; (2) developing, operating, and maintaining the NIH IMPAC system for the storage and retrieval of information of PHS extramural grant and contract programs; and (3) developing, preparing and issuing various reports to the initial review groups and institutes/divisions necessary for or related to the review and award process. The following items highlight significant projects relating to the overall Section responsibilities:

Impounded Fiscal Year 1973 Funds. Special procedures were developed in the Section to process awards issued from the released Fiscal Year 1973 impounded funds. The IMPAC System's update program edit criteria were modified to accommodate to the various ways the institutes are awarding these grants. New Common Accounting Numbers for the impounded funds were added to the IMPAC central table look-up system. A new data item called "impounded funds" was added to the IMPAC Open/Pending file to identify grants issued from the Fiscal Year 1973 impounded funds. The new item is to be used in responding to inquiries about these funds.

Resumé of Transactions. A new system for distributing the Research and Training Grant Resumes of Transactions (ROT's) has been installed by the Data Processing Section. This new system employs the use of a computer-based address file and the Cheshire labelling method. The labels are prepared by computer on special paper and mechanically affixed to the cover sheets. The resumes are prepared in the Section and sent to the print shop for duplication along with the labelled cover sheets. After duplication, the ROT's are collated with the cover sheets and sent directly to the mail room for distribution. Prior to the advent of this system, thermofax labels, which were manually affixed, were used for ROT distribution. This method required approximately 44 hours of DPS employee effort each month, whereas the Cheshire method requires only 2 or 3 hours.

IBM 3330 Direct Access Storage Facility. The Section converted its computer files from an IBM 231 Direct Access Storage Facility to the larger capacity IBM 3330 Direct

Access Storage Facility. As a result of this conversion, the on-line storage capacity of the IMPAC System's files has increased from around 466 million bytes to over 800 million bytes. This increase in storage capacity enables additional IMPAC files to reside on-line and greatly facilitates processing.

Manpower Report System. A computer file was established for recording data contained in the new Manpower Report Form (NIH-1749). These data are to aid NIH in annually accessing the input of its research support on the Nation's biomedical and health related manpower. Two files will be maintained: (1) IMPAC-Open file to establish and maintain internal processing control (mailing, receipt, follow-up, and so on) and (2) Manpower Report file to store and report data on personnel who performed salaried and unsalaried work on research projects. Information stored includes such items as number of persons; manweeks of effort; and dollars. Personnel working on the project are also grouped by levels such as Professional - Non-Faculty; Professional - In Training; Clinical Supporting Staff; Technical; and so on.

Committee Management Information System. A new Committee Management Information System containing information on NIH public advisory groups became operational in Fiscal Year 1974. The System maintains complete and up-to-date records on all NIH Advisory Councils and Committees and their members. It includes the processing of all documents concerned with the establishment, appointment of members, utilization, operation, and termination of NIH Committees; editing completed file for the semi-annual "NIH Public Advisory Groups" and other publications; and consulting with the Committee Management Office, OD, NIH, in developing procedures and handbooks. The computer system consists of two files. The Committee File contains information on the establishing authority, statute number, number of positions authorized, number of scientific positions authorized, budget, date established, and other information of the Committee itself. The Appointment File contains biographical information on each of the committee members.

Combined Research/Contract Narrative File. The Section is gathering detailed information and creating specifications to allow the combining of narrative data from contracts and research projects into a single file. This file is ultimately expected to be incorporated into the routine query processes of the Research Documentation Section providing added reference to scope and objectives of projects in addition to general grant and key term information.

Modifications made to IMPAC System during the year.

- (a) The Abbreviated File, a reduced version of the Pending/Open File, was established on line. The file is made up of items that have a high probability of being used in reports. The principal advantage of this file is that it can be queried through the "B" Initiators by all users and provides them with faster turn-around at computer cost savings. The savings are realized because the file size has been reduced, which results in a reduction of search time.

- (b) Department codes were established in the IMPAC System for schools of higher education to provide consistency in reports using department names.
- (c) Other items of data added to the system were sex code of investigators, 11 awarded budget categories, manpower control code, and impounded funds signal.

3. Research Documentation Section (RDS). The Section maintains a computerized disk storage and retrieval system, CRISP (Computer Retrieval of Information on Scientific Projects) containing scientific data on the research grants and contracts supported by the Public Health Service. Through this medium, RDS functions to service ad hoc and recurring requests for scientific information from Government administrators, scientists, and information personnel for purposes such as analysis and evaluation of research programs, specific scientific areas, and preparation of reports. In similar fashion, the Section responds to inquiries from grantee and non-grantee institutions and scientists, the news media, and other non-Government individuals engaged in, concerned with, or reporting on medical research.

The Research Documentation Section publishes annually as a "spin off" of the CRISP file:

- (a) The Research Grants Index, which is prepared in two volumes. Volume I is a scientific subject index with associated project numbers and titles. Volume II contains three sections (a) project identification data (2) research contract identification data and (3) project investigator information.
- (b) The Medical and Health Related Sciences Thesaurus, the vocabulary authority list of subject headings used by the RDS Indexing Staff in indexing the research projects.

CRISP has the query capability of providing information ranging from a straightforward listing of grants pertaining to a single scientific subject term to a compendium of projects relating to any number of terms, using a combination of Boolean search logic. Select queries for providing individual institutes with tapes or hard copy of their projects by subject, project (subproject) number of investigator, and individual institute listing of projects with indexing terms (Scientific Profiles) can be provided. Query capability limiting subject searches or Scientific Profiles to certain program (R, M, N, P, S) or IPF Codes is available.

In addition, performing subject searches and producing Scientific Profiles or investigator listings on subprojects of program projects, center and other large grants is a unique feature of the CRISP system.

A number of innovative features added to the CRISP System that have expanded its capabilities and streamlined operations include: (1) computer printout of individual project Scientific Profiles, immediately after indexing, on all type 1 (new) projects for mailing to the Principal Investigators. This has eliminated the laborious task of manually

typing the same information; (2) a new grant query format designed to print the term number to the left of each indexing term, for streamlining editing operations; (3) improved query logic, which provides greater ease and versatility of query formulations and output on subject searches; (4) inclusion of IPF Codes in the CRISP System, which allows for production of Institution Scientific Profiles by a single query rather than the cumbersome method used previously; and (5) computer preparation of Volume II of the Research Grants Index. (The Section is indebted to the Data Processing and Systems Planning Groups of SAB for providing the program and query logic, which made these cost reducing procedures possible.) Other improved operations in the Section include a fully automated mailing list file for the Research Grants Index.

Research Grants Index. For the first time the preparation of the Research Grants Index has been fully automated. Linotron tapes of both Volume I and Volume II were submitted to the Government Printing Office in December for publication (DHEW Publication No. (NIH) 74-200) in April 1974.

Medical and Health Related Sciences Thesaurus. A revised edition of the Thesaurus was published and distributed on a request basis. Since the demand far exceeded the number of copies available last year, additional numbers of the current edition were produced.

CRISP Services. The dramatic increase in both the number and variety of inquiries for CRISP services is noteworthy. In addition to responding to hundreds of routine inquiries, the Section: (1) prepared Linotron tapes used in the creation of "miniature" Indexes for three institutes; (2) produced Institute Scientific Profile data reports for two institutes; and (3) furnished NIH-wide scientific program area data to responsible institutes.

An inexpensive method developed by the Research Analysis and Evaluation Branch links CRISP data with project narrative tapes, and substantially increases the options available to the users of the CRISP System by providing project summaries (upon request) on demand searches. Further refinements of this capability are planned, which will incorporate narrative data directly into the CRISP System in a unified format.

4. Reports and Data Evaluation Section. The primary function of the Reports and Data Evaluation Section is the collection, storage, computer retrieval, presentation, and analysis of data on the extramural programs of the NIH and PHS for use in policy consideration, program planning, program analysis, and program management. In addition, the Section is responsible for the coordination of responses to inquiries about the extramural programs received from the Executive and Legislative Branches of the Government and non-Government sources.

Publications. The following volumes of the annual multi-volume series on PHS Grants and Awards were issued:

- (1) PHS Grants and Awards: NIH Health Manpower Education, Part IV, and Food and Drug Administration, Part V, Fiscal Year 1972 Funds.

- (2) PHS Grants and Awards: NIH State and Organization Summary Tables, Part VI, Fiscal Year 1972 Funds.
- (3) PHS Grants and Awards: Health Services and Mental Health Administration, Part VII, Fiscal Year 1972 Funds.
- (4) PHS Grants and Awards: NIH Research Grants, Part I, Fiscal Year 1973 Funds.
- (5) PHS Grants and Awards: NIH Training, Construction, Medical Libraries, Part II, Fiscal Year 1973 Funds.
- (6) PHS Grants and Awards: NIH Research Contracts, Part III, Fiscal Year 1973 Funds.
- (7) PHS Grants and Awards: NIH Health Manpower Education, Part IV, and Food and Drug Administration, Part V, Fiscal Year 1973 Funds.
- (8) PHS Grants and Awards: Health Services and Mental Health Administration, Part VI, Fiscal Year 1973 Funds.

The timely publication of the complete Fiscal Year 1973 series during the current year was an unprecedented accomplishment which greatly relieved the pressure for special reports and tabulations to answer inquiries on support to particular individuals, areas, and institutions.

Data for the pocket reference book, Basic Data Relating to the NIH—1974, were compiled in cooperation with the NIH Office of Program Planning. This publication presents information on the programs and resources of the NIH.

Special Statistical Presentations. The Section compiled and analyzed extramural program statistics for Fiscal Years 1967-1973, and participated with the Chief, Statistics and Analysis Branch, in developing a set of overhead projection slides illustrating key extramural trends. These slides were presented formally to the Director, NIH, and other officials in July 1973, and subsequently to various additional audiences. The data were also issued, with an accompanying analysis, in a chart-book entitled, NIH Extramural Trends, Fiscal Years 1967-1973 for administrative use.

Reporting Activities. There are several major reporting activities which are recurring or cyclical and consume a large portion of the man-hours available in this Section. The annual survey conducted by the National Science Foundation entitled Federal Funds for Research, Development and Other Scientific Activities is coordinated and prepared by this Section for the entire NIH. In general, the survey covers all the NIH intramural and extramural research activities for the past fiscal year along with estimated obligations for the next 2 fiscal years, by performer, field of science, geographic area, basic and applied research and development, and combinations of the above. A segment of the report is also devoted to "Scientific and Technical Information Activities."

The CASE Report is an annual survey on support to institutions of higher education and other nonprofit organizations. The NIH response to this survey is coordinated and prepared by this Section. It requires an institution-by-institution report of all NIH extramural support, by program, for most nonprofit organizations, with an individual report for each health professional school. In addition, data by field of science grouping are also requested for institutions of higher education by program.

The HSMHA portion of this survey was also prepared by this Section for those programs that are regularly processed by DRG.

Obligations for Medical and Health-Related Research and Training Activities is an annual survey of all Government-sponsored medical research and training. The NIH response to this survey is also coordinated and prepared by this Section and requires data on intramural and extramural research and development, by field of science, performer, programs, and state. Additional NIH data required include manpower statistics related to graduate training grants, fellowships, and research career program awards, by degree sought, by institution, by field of science and by institutional versus individual support.

At the beginning of each review cycle for research and training grant applications, statistical reports are prepared which present data on the number and dollar value of applications received for review. The presentation is by institute, fiscal year of support, and type of application. Copies are distributed to each institute/division. In addition, statistical tables showing summaries of initial review group actions on research and training grant applications are prepared twice during each review cycle for use by the Office of Financial Management, the institutes/divisions, and the Office of Research Manpower, DRG.

Inquiries. The Section responds to hundreds of requests for information each month from Federal agencies, NIH officials, other Government and non-Governmental organizations. These requests are primarily for statistical and analytical information concerning the NIH grants and award programs and characteristics of grantee institutions contained in the IMPAC system.

The inquiries range in complexity, as measured by man-hours, from several hundred to less than one per project. The Section has devoted considerable effort to the development of shelf, or reference listings, unpublished reports, and microfiche, to answer such inquiries. The Inquiry and Reporting System (a computer software facility) is the primary method for data extraction, manipulation, and hard-copy presentation of the information requested. About 8,000 queries were processed through the Inquiry and Reporting System for this purpose during fiscal year 1974.

Institutional Research. The Section has the responsibility for establishing and maintaining the Institution Profile File (IPF). The IPF is the central registry of names, locations, geographic and other selected data for organizations participating in the Public Health Service extramural programs. This file is the single source for organizational information established to assure uniform reporting and to eliminate the necessity for storing similar information in individual grant and award files. In Fiscal Year 1974, over 1,500

new institutions were added to the IPF. The IPF now contains about 20,500 records on institutions participating in NIH programs, as well as the programs of the Food and Drug Administration and other agencies of the Public Health Service.

During the year, a system for coding academic departments became fully operational, enabling consistent and accurate presentation of department names in academic institutions. The system was also used to select and tabulate records for specific kinds of departments, such as "surgery."

Retrieval Methodology. Three iMPAC Inquiry and Reporting System (IRS) courses were offered by the Section. A total of 35 persons attended two basic courses, and an additional 6 attended a course in advanced applications. IRS is the primary instrument for extracting and reporting IMPAC data.

About 8 consultations are handled each day for DRG and institute/division personnel needing assistance in debugging queries, developing more advanced queries, and applying new techniques.

Retrieval Applications and Procedures (RAP) has been developed as an informal, technical handbook to provide users with accurate information and instructions on how to apply new or more efficient retrieval procedures, and to correct recurring IRS problems. About 60 copies are distributed to DRG and institute/division personnel responsible for compiling IMPAC data.

Graphic Arts. Approximately 1,100 pieces of graphic art work were completed by the Illustrator in Fiscal Year 1974. The bulk of this work included: cover designs, charts, certificates, slides, signs, visuals, special exhibits, and illustrations for flyers and handbooks. Other major assignments involved the development and preparation of slides for various statistical presentations by the Director, NIH, and other officials. The Illustrator was also responsible for the artistic preparation and assembly of the chartbook entitled Extramural Trends, Fiscal Years 1967-1973.

5. Special Projects and Surveys Section. Fiscal Year 1974 was the Section's second year of existence as a formally established part of the Statistics and Analysis Branch. Its work focused on the collection and analysis of data concerning NIH extramural programs as aids to program operation and management. Performance of this function involved conducting surveys, designing and preparing special evaluation studies, making analytical reports, and developing appropriate computer systems.

Research Grant Expenditures. A computerized data base of the Report of Expenditures (ROEs) for Fiscal Year 1971 NIH research grants was established. This is the first comprehensive collection of expenditure data from these forms undertaken for all of the NIH. The data base combines the information reported on the ROE form that is submitted to the NIH by grantees with pertinent data from the IMPAC file. Data input and table programming were performed by a contractor funded under the NIH Health Evaluation Program.

The computer file is maintained by the Section and data from it can be made available to those having an interest in this aspect of the extramural program. Special computer systems have been developed for ready access to the file. The Section is developing similar data bases, with the assistance of contract funds available under the NIH Health Evaluation Program, for Fiscal Year 1972 and Fiscal Year 1973 expenditure data. Information for several years will permit analyses of trends in the spending patterns of NIH research grant recipients.

Two analytical reports on the Fiscal Year 1971 expenditure data were prepared and distributed to those concerned with extramural management. In addition, a presentation utilizing graphic slides was designed and given before groups of key personnel. These briefings not only provided those attending with information on expenditure patterns but informed them of the varied data available from the computer file. As a result there have been continuing requests for special studies to meet individual needs. In addition, the data from the Fiscal Year 1971 expenditure study are being used in the development of a manpower allocation model sponsored by the National Science Foundation for federally-funded research.

Biomedical Research Price Deflator. Analysis of the expenditure data called for use of a specialized statistical tool to provide a measure of the purchasing power of current dollars in relation to dollars of an earlier period. Comparison was made with expenditures for Fiscal Year 1966 for which data from a sample survey were available. Extensive investigation was made of the various price deflators available for this purpose. The deflators were applied to the expenditures and an analysis made of the results.

The Office of the Director, NIH, has contracted for the development of a price index to meet NIH needs. The Fiscal Year 1971 expenditure data are being used by the contractor to develop such a biomedical research price deflator.

Annual Manpower Report. The staff of the Section performed the major part in planning and designing the new annual report form for personnel working on NIH research grants and contracts. This report will supply needed information on the manpower used in the performance of biomedical research funded by NIH. It will build upon and supplement the data from the 1970 manpower sample survey conducted by the Section. The initial distribution of the form to principal investigators and program directors was made in December 1973. The Section's staff has been the focal point for correspondence and telephone calls from grantees related to completion of the form. The staff also served as advisors on processing problems and on the design of future report forms.

Manpower Analysis. The analysis and preparation of special reports covering the data from the 1970 NIH Research Grant Manpower Survey continues. The survey planned and conducted by the Section's staff has proven a valuable data base, unique among the information resources of NIH. The work completed has been continuously used by institute and OD staff. The National Science Foundation impact and allocation model of federally-funded research by academic institutions is using the 1970 survey data as the basis for extrapolating biomedical research costs and manpower and developing FY 1972 estimates.

The development of the annual manpower report has increased the need for 1970 manpower data to serve as a basis for comparison. There are four 1970 baseline analyses that are presently at varying levels of completion. Two of these were prepared under contract funded by the Fiscal Year 1974 Health Evaluation Program.

Publications

NIH Research Grant Expenditures Fiscal Year 1971 - Part I. Special Project Report No. 1, January 1974.

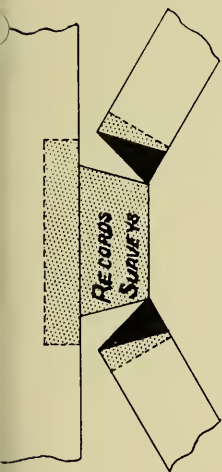
NIH Research Grant Expenditures Fiscal Year 1971 - Part II. Special Project Report No.2, June 1974.

HOW TO USE
THESE SEPARATORS

Use one page for
each separation.

Select appropriate
tab, add further
identification if
desired, and cover
it with scotch
tape.

Cut off and discard
all tabs except the
one covered by tape.



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ANNUAL REPORT

FISCAL YEAR 1974

(July 1, 1973-June 30, 1974)

DIVISION OF RESEARCH RESOURCES

National Institutes of Health
Bethesda, Maryland 20014

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REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

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Report of the Division Director

Fiscal Year 1974 has been one of further refinement and additional development of the multi-categorical biomedical research resources supported by the Division. This activity is reported on by the major program areas in the accompanying pages of this annual report.

This continued program development has taken place concurrently with, and against a backdrop of an internally initiated self-analysis of the objective, function, and structure of the Division of Research Resources.

In 1961, the Division of Research Resources (nee the Division of Research Facilities and Resources) was established with the objective to--

"support general purpose facilities and resources
and strengthen the general health research
capabilities of institutions."

During the period of 1968-1970, the DRR (while within the Bureau of Health Manpower) was assigned a status quo objective to--

"provide a focal point for the administration and
management of broad NIH programs intended to supply
a wide institutional base of support for health-
related research."

During the last half of Fiscal Year 1973, an internal DRR Task Force was established by my office to deal with a single question--"Can DRR broaden and strengthen the interrelationships among its variety of research resource programs in such a way that their individual and corporate actions will be even more effective in the future than they have been in the past?"

The Task Force developed and presented to the Division for debate, four candidate contemporary objectives (actions)* with accompanying assumptions and tentative derivative actions. During the first part of Fiscal Year 1974, the Division decided to select a single contemporary objective, i.e.:

- * 1. Make research resources exclusively "merit-driven."
2. Abet the sponsored activities of NIH's categorical programs.
3. Assist non-profit institutions in the development of their
biomedical research capabilities.
4. Facilitate the acquisition of new knowledge.

TO IDENTIFY AND MEET THE RESEARCH RESOURCE NEEDS
AND OPPORTUNITIES OF THE NIH INSTITUTES

by

conceiving, creating, developing, and insuring
the availability of those resources that are
essential for the efficient and effective conduct
of human health research.

During the latter part of Fiscal Year 1974, the Division's top management team and subteams were actively engaged in examining the needs of the contemporary objective as regards--

- the type of resource development system and organization;
- the type of grants management and processing system and organization;
- the type of technical merit review system and organization.

As we move into Fiscal Year 1975, we plan to continue to test our assumptions regarding the selected objective, i.e.--

- DRR can best serve the NIH by selectively concentrating its resource activities on the clientele of the categorical programs;
- DRR can set up machinery for program planning, analysis, and evaluation that is adequate to make DRR--and its clientele--highly responsive to the pace and direction of categorical programs, and to the resource needs of those categorical programs;
- DRR can get continuously up-to-date profiles of where and how the categorical Institutes commit their appropriated funds and an understanding of the rationale for these commitments;
- the Institutes and the OD, NIH would actively support such a contemporary objective.

DRR BRANCH REPORTS

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DRR BRANCH REPORTS

Fiscal Year 1974 Annual Report
Animal Resources Programs
Division of Research Resources

INTRODUCTION

The overall objective of the Animal Resources Branch is to support resource projects that provide, or enable biomedical scientists to effectively use animals in human health related research. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The Branch objectives are accomplished through a Primate Research Centers Program, a Laboratory Animal Sciences Program, and Research Contracts.

PRIMATE RESEARCH CENTERS PROGRAM

The Primate Research Centers, established with Federal funds in the early 1960's, continue to provide national and international leadership in the rapidly expanding field of biomedical primatology. The Centers, operated by grant funds, provide unique research environments where biomedical research in many important areas is being conducted. During this year, numerous contributions were made in the areas of metabolic and degenerative diseases, cardiovascular diseases, reproductive biology, infectious diseases, and neurological disorders.

The core support provided by this program permitted the 141 core staff scientists to conduct research on a total of 134 grants and contracts totaling \$7.4 million. As a result, 677 scientific papers and 53 books were published during the year. Some 484 collaborative scientists from a number of universities utilized these facilities to conduct research on 191 NIH supported grants and contracts totaling \$14.0 million. The Centers were active in both research and professional training with 127 graduate students participating in the research activities. Three veterinarians and two veterinary pathologists received special training in primate medicine and pathology. The program provided salary support for 162 doctoral level staff and 680 technical and administrative personnel.

The Centers, realizing that primates are difficult to obtain from their native habitats, are taking steps to breed the animals required for their research programs. During the past year, a total of 1,110 infant monkeys were produced in the Centers for use in the research programs. It is estimated that the Centers are now producing 50% of their annual requirements. The Centers are also maintaining small nuclear breeding colonies of some 24 less commonly used primate species in order to assure their survival for future biomedical research purposes.

The missions and selected research activities of the Centers are as follows:

OREGON PRIMATE RESEARCH CENTER

The missions of this Center are reproductive biology, cardiovascular and metabolic diseases, and immune diseases. The following are examples of their research accomplishments:

1. Triggering the Onset of Labor

It is not known whether the full-term fetus is a self-starter or if some maternal or placental mechanism precipitates labor. An answer to this question will greatly help clinicians in dealing with the medical problems of premature labor and postterm retarded onset. It is known that anencephalic infants often have long gestation periods, suggesting the pituitary gland is an essential factor in the regulation of the onset of labor. A technique has been devised for functionally removing the pituitary of fetal rhesus monkeys at midpregnancy and thereby in effect, inducing anencephy. The overall growth of the fetuses is markedly retarded, and the endocrine glands are only one-tenth normal size. These results show that the fetal pituitary is essential for normal development and that the hormones of the maternal pituitary do not cross the placenta. This new way of exploring the role of the primate fetal pituitary during gestation may lead to the development of endocrine therapy for human fetuses before birth.

2. Cholesterol Gallstones and Atherosclerosis in Squirrel Monkeys

Cholesterol gallstones involve more than 5 percent of the total U.S. population and a much higher percentage of certain groups. This affliction has a high dietary cholesterol intake as a common feature with atherosclerosis, a disease responsible for over half of the deaths in the U.S. However, the populations with the highest incidence rates for each of these diseases is different. Studies on the cause of gallstones in experimental animals are intrinsically valuable per se, but may be even more valuable in elucidating the much more important problem of atherosclerosis. It is particularly important to know the treatment of each disease affects the development of the other. An animal model for studying gallstones has not been available; however, recent investigations have shown that gallstones consistently form in the squirrel monkey. The composition of diet determined the prevalence of gallstones. These studies on the squirrel monkey were the first to describe a consistent nonhuman primate model for induced gallstones and to systematically investigate the nutritional and individual factors that influence stone formation. Monkeys fed diets containing cholesterol in proportions similar to those in an opulent human diet develop a level of cholesterol in their blood plasma similar to that of people. They also have a 50 percent chance of developing cholesterol gallstones after one year on the diet. Studies on squirrel monkeys may prove helpful in devising nutritional methods or drugs for preventing or dissolving cholesterol gallstones without accelerating the process of atherosclerosis or any other unfavorable side effect.

DELTA PRIMATE RESEARCH CENTER

The primary mission of this Center is infectious diseases, and examples of their research activities are as follows:

1. Cancer Virology

The virus complexes that have been isolated from lymphomas of monkeys are being studied, and methods to grow and detect these viruses in cell cultures have been developed. Attempts are being made to reproduce the disease by inoculating young monkeys. This Center is also studying a monkey virus that closely resembles the virus causing infectious mononucleosis. In some monkeys, this virus causes tumors, while in the squirrel monkey it produces a benign infection. The defenses in the squirrel monkey that prevent tumors are being investigated.

2. The Chimpanzee as a Model for Serum Hepatitis

Serum hepatitis has been an increasing health problem over the past decade, especially for patients requiring frequent blood transfusions. Research has been hampered as no laboratory animal was available to study this disease. Recently, it has been shown that the chimpanzee is an excellent animal model for serum hepatitis. Experimental inoculations with human serum from hepatitis patients have been made in order to determine the relative virulence of the various subtypes of serum hepatitis. It is hoped that this research will lead to the development of a vaccine for this disease.

YERKES PRIMATE RESEARCH CENTER

The mission of this Center is neural and behavioral research and the study of neoplastic and degenerative diseases. This Center has the largest colony of great apes available anywhere in the world for biomedical research.

1. Chimpanzee Language Study

Considerable progress has been made in this project during the past year. A young chimpanzee in a computer-controlled language training situation has revealed impressive capabilities for the acquisition of language skills closely related to those employed by men in their languages. The chimpanzee, after only one year of training has learned to a) read and finish sentences validly started, b) that objects have names and c) to give the name of familiar objects with great facility. This animal has demonstrated the ability to equate projected pictures of objects with physical objects. This work serves to reinforce the assertion that the chimpanzee in all ways is closely related to man and to underscore the possibility that the apes might be used as subjects in radical experiments designed to explore the conditions germane to the acquisition of language by the human child.

2. Experimental Chimpanzee Breeding on Ossabaw Island

A group of four female chimpanzees, one male and one juvenile, have been established on Bear Island, one of the Ossabaw group situated 20 miles south of Savannah, Georgia. The object of this experiment is to determine if they would survive year round in the open and whether they would breed under these circumstances. The study has already shown

that the animals can survive the winter, and the recent birth of a young chimpanzee suggests that they will be able to breed successfully on this island. This study is of special importance due to the growing shortage of chimpanzees for biomedical research and the danger that in the near future it may be impossible to obtain these animals from their native countries.

WASHINGTON PRIMATE RESEARCH CENTER

This Center continues to pursue its original missions, namely neurophysiology relating to cardiovascular function and the development of an extensive collaborative research program involving a large number of scientists in many biomedical research disciplines. The following are examples of research being conducted at this Center.

1. Arterial Smooth Muscle Cell in Atherosclerosis

A new hypothesis of how atherosclerosis is produced has been formulated by using tissue cultures of arterial smooth muscle derived from pigtailed monkeys. At an early stage in the development of atherosclerotic lesions, smooth muscle cells increase in the intima of affected arteries, probably as a result of cell proliferation. This increase is accompanied by the formation of various extracellular connective tissue components. In addition, lipids, particularly cholesterol and phospholipid, accumulate within smooth muscle cells causing them to develop the appearance of "foam" cells. It is this increase in smooth muscle cells, connective tissue, and lipids that forms the atherosclerotic "plaque." The series of events that give rise to the initial changes in arterial smooth muscle is poorly understood. The development of these new techniques using the pigtailed monkey will hopefully shed light on the causation of this important disease.

2. Auditory Physiology

The physiological mechanisms underlying hearing dysfunction have been studied in rhesus monkeys using environmental factors such as conductive hearing losses induced by middle ear pressure changes, receptor dysfunction induced by noise trauma and drugs such as aspirin; and hearing changes from central auditory dysfunction induced by tumors. These studies on nonhuman primates have allowed the investigators to develop an animal model of human function in which biomedical questions regarding hearing loss can be investigated. Efforts have been made to compare measures of function under similar conditions in man and monkey. These measures now permit an evaluation of physiological function and to define hearing losses induced by experimentally controlled pathologies.

WISCONSIN PRIMATE RESEARCH CENTER

Neural and behavioral sciences and reproductive biology are the basic missions of this Center. Examples of the research accomplishments are as follows:

1. Effects of Noise on Behavior

Rhesus monkeys were exposed to recorded sounds such as jack hammers and hard rock music at the level of 100 decibels for five-hour periods. During exposure, the monkeys' behavioral syndrome was marked by four distinct phases. The animals typically displayed hyperactivity with the onset of noise stimulation. Following the hyperactive phase, the monkey subjects engaged almost exclusively in oral and tactile exploration of the test chamber. After one hour of exposure their behavioral profile reflected passivity and general inactivity. The monkeys maintained a sitting posture with eyes fixed on one object. During the last one or two hours of the five-hour treatment they assumed a prone position and became behaviorally inactive. These animals were exposed to high decibel levels for shorter duration than humans often experience. Typists live in an environment of 80 decibels, and many factory workers are often subjected to continuous levels of noise over 100 decibels each day. Humans subjected to long, loud noises display some effects similar to those noted in monkeys. The long-term effects of high noise levels in humans need to be explored further.

2. Effects of PCB's on Monkeys

Adult monkeys appear to be more susceptible than infants to the injurious effects of PCB, a commercial industrial chemical. Adult rhesus monkeys fed moderately high levels of PCB for three months lost weight and hair, had enlarged livers and drastic changes in the bone marrow. Infant animals receiving the same levels showed none of these symptoms. PCB's are stored in body fat, and since infants have little fat, there are fewer cells to deposit these compounds. In addition, the livers of infant monkeys are apparently unable to break down PCB, and, therefore, it passes through the body unchanged. Livers of adult animals convert PCB to more harmful compounds which causes the symptoms noted in this experiment. Research of this nature will lead to a better understanding of the effects of environmental chemicals on humans.

NEW ENGLAND PRIMATE RESEARCH CENTER

The core staff are conducting research in the areas of infectious diseases and primate pathology. In addition, a number of collaborative scientists from several institutions conduct a major portion of their research activities at this Center.

1. Primate Model of Drug-Seeking Behavior

Collaborative investigators working at the Center with several primate species are investigating the acquisition and maintenance of orderly sequences of behavior leading to the injection of drugs. They are conducting experiments to analyze the behavioral and pharmacological factors that determine whether a drug will maintain, suppress or have little effect on behavior that precedes its injection. Recent experiments show that long, orderly sequences of key-pressing

behavior can be maintained in primates when behavior results in a single daily injection of morphine or cocaine. The model of drug-seeking behavior in primates is analogous to drug-seeking behavior in humans. The successful development of this model makes it possible to study the effects other drugs and behavioral procedures may have on drug-seeking behavior in humans.

2. Recent Developments in Herpesvirus Research

Experiments conducted at this Center have proven for the first time that the spider monkey is the reservoir host for several strains of Herpesvirus ateles. Some of these strains have oncogenic properties. Herpesvirus saimiri has been isolated from natural leukemia in owl monkeys, and it has been found that this strain is more oncogenic than the prototype strain isolated from squirrel monkeys. These studies add to our knowledge of the oncogenic properties of Herpesvirus in primates and provide a model for the study of human Herpesviruses.

CALIFORNIA PRIMATE RESEARCH CENTER

The mission of this Center is in the areas of infectious diseases and environmental health sciences.

1. Birth Defects in the Nonhuman Primate

It has been demonstrated that the nonhuman primate is the animal model of choice for the study of many birth defects in man. This is particularly true regarding the effects of certain environmental chemicals. It has been shown that triamcinolone is quite teratogenic resulting in skeletal changes and cleft palate. Such studies not only provide valuable knowledge on the effect of such drugs in pregnant women, but also provide a laboratory model for the scientific study of the mechanism of drug action.

2. Model for the Study of Bacterial Pneumonias

A primate model has been developed recently in which pneumococcal pneumonia can be reliably induced. The induced infection produces sufficient quantities of intrabronchial secretions to allow measurement of antimicrobial concentrations. This Center now has a choice of animal model to study the therapeutic efficacy of antimicrobial agents commonly used in man such as penicillin, ampicillin and several others.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants. Currently active program areas include support for animal colonies of unusual and special value for research; studies directed at finding animal models which are needed for research on human diseases; projects to assist institutions

to comply with the legal and policy requirements for care of laboratory animals; laboratories for the diagnosis and control of disease of laboratory animals; research related to improving health care and determining environmental requirements of animals used in research; reference and information centers dealing with selected problems; and training of specialists in the field of laboratory animal medicine. The program awarded funds totaling \$7.505 million in fiscal year 1974, which supported 96 discrete animal research and resources projects, 6 training programs, 13 fellowship awards, and 5 contracts.

ANIMAL MODELS AND SPECIAL COLONIES

The major objectives of this program area are (1) to characterize and define biological attributes of selected animals which display potential for rather broad biomedical research application; (2) to establish, improve and/or expand special colonies of well-defined animals which are of proven value for specialized research areas, but which are not generally available from other sources; and (3) to preserve unique and valuable animal stocks and strains which may otherwise be lost (e.g., because of temporary lack of project support).

Support for projects related to the development of research animal models and the establishment of special colonies of valuable research animals has remained quite static during the past several years, with 22 projects supported during FY 1974 (approximately \$1.250 million) as compared to 20 projects supported during FY 1973 (\$1.141 million) and 21 projects active during FY 1972 (\$1.250 million).

The vast majority of active projects in this area are related to vertebrate species (e.g., rats, mice, guinea pigs, hamsters, degus, rabbits, Arctic rodent species, frogs, armadillos, dogs, zoo animals, nonhuman primates, etc.). However, increased attention has recently been given to the support of model development and/or special resources of appropriate invertebrate animals, e.g., Xyleborus (wood-boring beetle) and rare species of Drosophila for use in several areas of biomedical research activities. As a result of planning during the past year, contract efforts will be initiated in June 1974 on the development of laboratory mariculture techniques for Aplysia (sea hare) and/or related marine gastropods (i.e., Hermisenda and Pleurobranchaea). These marine invertebrate organisms are used extensively in several biomedical research areas, and their uncertain availability and quality from natural marine sources has presented problems of increasing severity.

Projects related to the characterization and development of new animal models have been limited to those strains and species for which there is evidence of good potential utility for activities in several research disciplines or disease categories. Efforts of investigators of several disciplines over a rather extensive period are usually required to fully exploit the potential of such animals as useful models.

Examples of animal model development projects which are currently supported by the Program include (1) a colony of degus (University of

Vermont) with unique biological attributes for studies in the areas of immunology and eye cataract development; (2) germfree mice and rats (University of Notre Dame) under development as potential model systems for studies on cancer therapy, environmental pollutants, and gerontology; (3) an inbred colony of cats (Washington State University) which possess a number of interesting chromosome anomalies being studied as models for Turner's syndrome, dwarfism, Klinefelter's syndrome, and demyelinating diseases; (4) a newly acquired colony of Syrian hamsters (Massachusetts Institute of Technology) which are under development for use in a multitude of biomedical research areas including genetics and cancer research; and (5) studies on cats (University of Alabama Medical Center) which represent potential new models of neurological disease.

Examples of ongoing projects which provide support for maintenance of special colonies and serve as institutional and/or national resources include (1) an inbred rabbit colony (University of Illinois College of Medicine) which supports a large research program for investigators of immunotherapy; (2) germfree dogs (Louisiana State University College of Medicine) for studies on human encephalopathy, stress ulcers and other diseases; and (3) colonies of several species of amphibians which are being studied at the University of Michigan to develop new techniques and knowledge to solve problems related to laboratory housing, husbandry, and breeding. During FY 1974, 11 of these special colony resources undergirded 55 NIH-funded research projects with a total funded value of \$3,614,000 and 39 other biomedical research projects which received funding from other sources (total research funding value of \$750,000).

Five institutional primate resource grants constituted an additional group of special animal colonies which were used for support of multidisciplinary biomedical research programs within institutions. Four of these grants have reached their natural termination during FY 1974, after becoming firmly established resources. The value of these resources has been well demonstrated in the past. For example, during FY 1973, active primate resources supported by the Laboratory Animal Sciences Program (LASP) were utilized in support of 95 NIH research grants with a total funded value of \$8,559,000. In addition, these resources were used to support 27 projects funded by other sources (total funded value of \$1,396,000). Support of the initial establishment of primate resources of this nature will remain as an eligible area in the Program.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Upgrading of existing animal facilities and development of new centralized animal resource programs has continued to be the most active program area. Requests in this area usually include animal cages to meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource. The amount of funded research involving the use of animals and the sources of funding are important factors in establishing funding priorities. The Program

Analysis Branch has identified 1,122 projects (\$64 million current annual funding) involving the use of animals which are supported by NIH at those institutions with currently active resource improvement projects.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program; however, they received increased emphasis beginning in FY 1972 when Congress appropriated an additional \$1.5 million. These funds were added to the regular budget to help research institutions achieve compliance with the Animal Welfare Act of 1970 (P.L. 91-579). The NIH policy on "Care and Treatment of Laboratory Animals" (issued June 14, 1971) and the subsequent DHEW policy on "Animal Welfare" (issued May 14, 1973) also contributed to the overall response in this area. The following figures demonstrate the progression of support:

	<u>FY 1971</u>	<u>FY 1972</u>	<u>FY 1973</u>	<u>FY 1974</u>
No. of Improvement Projects	14	24	28	46
Dollars Awarded (in \$1,000's)	673	2,169	2,318	3,217
Percentage of LASP Budget	11%	35%	37%	55%

In addition to those projects which were funded, a large backlog of approved, unfunded applications developed. During the current fiscal year (FY 1974) there was some reduction in the number of new improvement applications which were received and reviewed (19, of which 12 were recommended for approval). Thirty-four (34) new awards totaling nearly \$3.0 million were made. This included 5 new projects (\$583,000) which were funded during the year with impounded funds released from the FY 1973 budget. Thus, a considerable number of projects approved in prior years have been funded. However, there will be 19 approved applications (requesting approximately \$2 million) which will remain unfunded. A number of these date back nearly two years and will be administratively withdrawn. This will allow those institutions with a continuing need to update and improve their proposals. Continuing inquiries from additional institutions indicate that requests for assistance in this area can be expected to continue at about the current level for the next several years.

DIAGNOSTIC LABORATORIES

The objectives of these laboratories is to provide for improved animal health programs through investigation of naturally occurring laboratory animal disease, to support indepth studies resulting in new information on disease processes and their etiology, to aid in the elucidation of new laboratory animal models of human disease, and to develop resources, including tissues, slides, photographs, etc., for research and training in laboratory animal medicine and comparative pathology. There are 13 programs which are currently being supported. A shortage of appropriately trained specialists (veterinary pathologists and microbiologists) has been a limiting factor, precluding any rapid establishment of new programs. However, three new laboratories were funded during FY 1974. Special attention is being given to laboratories which have the potential of

serving more than one institution. Several laboratories are now providing service to other institutions in the same metropolitan area or are serving a regional area. Programs of this type will help conserve resources and justify more sophisticated capabilities.

By undergirding an institution's animal health program, the laboratories make a direct contribution to approximately 1,138 NIH supported research projects using animals with total funding of nearly \$97 million. In addition to the service aspects of diagnosis, the laboratories have been productive in terms of new information and techniques. In-depth studies of laboratory animal disease problems resulted in over 70 publications and presentations during the past year. One laboratory compared the three generally accepted techniques for detection of microfilaria in canine blood. An assessment of the reliability, costs and time involved for large scale screening programs was obtained and as a consequence the effectiveness of the institution's quarantine and processing program was considerably improved. These results were published and are available for consideration by other institutions located in areas with a high incidence of heartworms. Collaborative studies at one institution revealed clear metabolic and histopathologic evidence of significant exposure to lead in wild rats trapped in a major urban area while rural wild rats were apparently not exposed to the same extent. This work is continuing with outside grant support and will extend existing information about the use of wild rats as models of environmental exposure to heavy metals. Initial observations of an atypical colonic hyperplasia of mice were followed up by another laboratory. They were successful in establishing the disease in susceptible mice (Swiss Webster) by oral inoculation of tissue culture fluids. Sufficient data were obtained utilizing the techniques of light and electron microscopy and cell kinetics employing autoradiography to successfully compete for a grant from the Large Bowel Cancer Program of the National Cancer Institute. One laboratory became extensively involved in studies of lymphocytic choriomeningitis (LCM) in Syrian hamsters and other animal species following an outbreak of LCM in hospital personnel. The source of infection was traced to a colony of hamsters being covertly maintained in a room outside the central animal facility. The room also housed a Xerox machine, and the traffic generated by it resulted in exposure and infection of a wide range of individuals in addition to those primarily concerned with the animals. Findings resulting from the study of this outbreak led to improved control of animal movement, additional isolation procedures, screening of animal tumors for zoonotic pathogens (imported transplantable tumors were implicated as the most likely source of the LCM virus), and the establishment of an Animal Research Safety Committee.

RESEARCH PROJECTS

The Program has provided support to a relatively small number of discrete research projects over the past several years. This may be summarized as follows:

Research Related to Animal Resources

	<u>FY 71</u>	<u>FY 72</u>	<u>FY 73</u>	<u>FY 74</u>
Number of Projects	4	6	8	10
Awarded (in thousands)	403	449	593	591
Percentage of Total \$	9%	7%	10%	10%

Projects falling into this category generally have one of the following objectives: (1) to investigate the etiology, pathogenesis, and control of laboratory animal disease problems, (2) to determine various environmental requirements of laboratory animals. For example, currently active projects include studies of sialodacryoadenitis in the laboratory rat, diagnosis and control of mammalian encephalitozoonosis, definition of environmental conditions for laboratory animals, and development of nonhuman primate embryo transfer. The latter project has made progress to date in developing the necessary techniques to recover embryos from mated females. The next step will involve embryo transfer to the uterus or oviduct of other females. If completed pregnancies can be obtained by these procedures, then an important tool for the production of selected animal research models as well as for the study of genetic diseases and teratology will have been developed.

REFERENCE CENTERS AND INFORMATION PROJECTS

The Program has continued to support several reference center and information projects. Examples of these are:

1. A Simian Virus Reference Laboratory at the Southwest Foundation for Research and Education, San Antonio, Texas. The Laboratory now has a working repository of over 60 virus reference reagents and reference antisera. Ongoing activities of the project are designed to give information regarding the immune status of subhuman primates and the possible cause of outbreaks of overt diseases. Institutions throughout the country have taken advantage of this program. For example, during the past year, 40 laboratories submitted over 3,000 sera from various nonhuman primates for B virus antibody testing. The Laboratory also provided considerable backup support to the Charles River contract (described under Research Contracts Section) by testing almost 1,000 sera against multiple antigens.

2. The Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology (AFIP). The Registry has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish and birds. Material has been made available to others and utilized for the preparation of exhibits, lantern and microscopic slide sets, and as the basis for a number of publications. In addition to publication of a quarterly "Comparative Pathology Bulletin," the Registry sponsors

publication of an animal model in each issue of the American Journal of Pathology. A handbook entitled "Animal Models of Human Disease" has been prepared for sale. The initial fascicle contained descriptions of 16 models and a second fascicle completed during the past year included 14 additional models. A three-day course in Comparative Pathology will be offered for the first time at the AFIP this May.

3. The Laboratory Primate Newsletter, which now has a mailing list of about 1,700 individuals and organizations. The Newsletter provides information on maintenance, breeding, and procurement of nonhuman primates for laboratory studies. It also serves as a general source of information through announcement of meetings, nomenclature changes, etc., and aids investigators by publishing requests for materials.

TRAINING

Training in laboratory animal medicine is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

The Animal Resources Branch has supported programs in laboratory animal medicine since 1967. At that time, six programs were transferred from the National Institute of General Medical Sciences, which initially supported training in this area. Eight programs were supported during the current fiscal year. This number will be reduced to seven beginning July 1, 1974. The programs are all located in medical research environments. Diagnostic laboratories are also supported in each of these locations, and the laboratory resources have provided major input to the training experience. In addition to the training grant mechanisms, the Branch has supported training through the award of individual postdoctoral and special fellowships. In some cases these individuals have enrolled in the ARB training programs. Approximately half of the individuals seek more specialized research training. These fellows have engaged in in-depth studies in a discipline or specialty such as surgery, pathology, virology or physiology, through which they can contribute to research animal resources.

Currently available figures indicate that 98 trainees and fellows have completed training since the inception of training grants and fellowships in laboratory animal science and medicine. Forty (40) of these are employed by medical schools and 34 by other academic, research or governmental organizations. The majority (55) are functioning as directors or staff members of a vivarium; 38 are engaged in research or are obtaining additional training; and 5 are engaged in public health and other activities. Retention in the field of laboratory animal

medicine has been excellent for these programs, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

A decision to phase out research training supported by the National Institutes of Health was reflected in the 1973 budget. This decision involved impoundment of a portion of the funds appropriated by Congress for training activities. Under the phase-out plan, no new trainees or fellows could receive appointments. A lawsuit initiated by the AAMC challenged this action and early in 1974 their litigation resulted in the release of funds impounded during FY 1973. For ARB this resulted in the release of \$141,000, which was awarded as a supplement to the ongoing programs in February. Accompanying this action was the notification that the prohibition on new trainee appointments was rescinded. Funds were provided in the 1974 Appropriation Act to support training at the restored level for the period July 1, 1974 -- June 30, 1975. However, it will take a considerable period of time to recruit new trainees and regain the former level of activity. The uncertainties regarding the future in terms of long-term continuation of federal support, stipend levels, etc., have made it very difficult for training program directors to operate effectively.

In the fall of 1973 a "new" Manpower Development Program was announced. ARB received approval to make awards under this program in the field of laboratory animal medicine and science, and \$140,000 was allocated for this purpose. The program is similar to the old postdoctoral fellowship program, but does provide for higher stipend levels. The deadline for receipt of application was February 1, 1974. Thirteen (13) applications are currently under review, and approximately 10 new awards can be made under this program beginning June 1, 1974. It is anticipated that the "old" fellowship program will be terminated as soon as the six active fellows complete their programs.

RESEARCH CONTRACTS

The Animal Resources Branch has used the research contract mechanism as an adjunct to its resource grant programs to support specific essential services or to initiate activity in vital resource areas that have not responded or are not eligible to respond to the grant mechanism. Research contract funds for ARB in FY 1974 were about \$500,000, including \$300,000 transferred from NINDS for support of the Caribbean Primate Center. Five projects were supported. In addition one project funded in FY 1973 was completed in FY 1974, and one was transferred to the Food and Drug Administration.

PARTIAL SUPPORT FOR THE INSTITUTE OF LABORATORY ANIMAL RESOURCES

The Institute of Laboratory Animal Resources (ILAR) is a subsidiary of the National Academy of Sciences, established as a coordinating agency to disseminate information, survey existing and required animal resources, establish standards and promote education in the field of laboratory animal science. Since July 1953, ILAR has received financial support

from NIH. These activities are a valuable adjunct to the Animal Resources Branch program. The ILAR meets ARB needs for writing standards and guidelines for animal facilities and care, furnishing information on sources and users of laboratory animals, and providing survey information on the status of animal resources. Special activities include an information service on the sources and availability of over 450 animal models and genetic stocks and a field survey on the abundance and distribution of primates of biomedical interest in selected areas in South America. Another special activity funded late in FY 1973 and active this year has been a survey and analysis of use of primates for research and a review of field study data on primate populations. The purpose of this study is to provide information for planning numbers and species of primates which should be bred in this country.

DOMESTIC, COMMERCIAL PRIMATE PRODUCTION

ARB has renewed for a third year a contract with Charles River Breeding Laboratories to provide partial support for determining the feasibility of domestic production of free ranging rhesus monkeys on an island in the Florida Keys. Although the need for this type of program has long been accepted, the low cost of imported wild-trapped monkeys, and long-term investment in a breeding program has discouraged commercial firms from developing this concept. NIH support has stimulated interest in this area and has helped assure a quality program. A change in the contract last year will give NIH first priority to obtain primates produced on the island, and this may be extremely beneficial to NIH because of reductions in the export quota of rhesus monkeys from India. About 350 primates have been placed on the island as of April 1, 1974, and it is expected that 200 more will go onto the island before July 1. About 20 infants were born this past year from the first group of 90 animals placed on the island in May of 1973.

AMERICAN ASSOCIATION FOR ACCREDITATION OF LABORATORY ANIMAL CARE

The Animal Resources Branch is providing through a small contract partial support for site visits at a number of institutions that were accredited by AAALAC 3 to 5 years ago. This effort is important to maintain quality in the accreditation program. NIH officially recognizes AAALAC accreditation as meeting the requirements of its policy on the care and treatment of laboratory animals.

MARICULTURE OF MARINE INVERTEBRATES

Late in the fiscal year the Animal Resources Branch awarded a contract for laboratory breeding and rearing of Aplysia and/or related species. This marine mollusk is used in a variety of biomedical studies and is becoming increasingly difficult to obtain from nature (the principal supplier now "rations" the animals to researchers). It is felt that with two to three years' effort it is feasible to establish laboratory culture of this species, thereby assuring a supply of high quality animals.

CARIBBEAN PRIMATE CENTER

This primate resource is being supported by funds transferred from the National Institute of Neurologic Diseases and Stroke, which formerly supported the Center. The Center includes several semi-free ranging primate colonies on islands off the coast of Puerto Rico. The Center is a valuable resource for research on social behavior and neurologic behavioral relationships and has the potential to be an important breeding center. The breeding potential was in part realized in FY 1974 as the Bureau of Biologics, FDA, awarded a contract which supports production of 500 rhesus monkeys per year.

DEVELOPMENT OF A TRAINING PROGRAM FOR ENTRY LEVEL ANIMAL CARE TECHNICIANS

This project with the University of California San Francisco Medical Center came to successful completion in FY 1974. Its purpose was to develop training materials to instruct entry level animal care technicians. A series of 30 audiovisual lessons, with accompanying students and instructors manuals, was developed. Field tests indicate the program will be highly successful. The materials are now being readied for distribution by the American Association for Laboratory Animal Science.

HOLLOMAN PRIMATE FACILITY

In previous years the Animal Resources Branch had a contract to provide basic support for a large chimpanzee colony and other primates formerly supported by the Air Force at Holloman Air Force Base, New Mexico. Responsibility for this contract has now been transferred to the Bureau of Biologics, FDA, because it is closely related to another contract from that agency for chimpanzee breeding and hepatitis research.

ADMINISTRATION

A major administrative activity in fiscal year 1974 has been the development of a National Plan for Rhesus Monkey Supply. Rhesus monkeys are the pre-dominant species of nonhuman primate used in biomedical activities. Early in the fiscal year we were informed that the government of India was considering a 40% reduction in the number of rhesus monkeys it would allow to be exported (reduction from 50,000 to 30,000). This was later confirmed and we were asked by the Director of NIH to develop a plan for rhesus monkey supply. The plan we developed features both conservation of use and domestic production of primates. We have held meetings with the Federal Interagency Committee on Animal Resources and a group representing the Health agencies of DHEW to discuss the primate supply situation and means of conserving their use. We have also notified all recipients of rhesus monkey certificates of the problem and asked that they reduce their use of rhesus monkeys. Overall, the biomedical community is well aware of the problem and is concerned about it. We have scheduled a meeting with representatives of the pharmaceutical industry in June to discuss the problem with them and to enlist their

efforts in conservation of animals and domestic breeding. We have also developed a plan for domestic breeding to meet part of the NIH extramural requirements. Funds have been reprogrammed to the Division of Research Resources to initiate this program through a primate breeding contract awarded late in FY 1974.

A second major administrative effort in fiscal year 1974 was to complete work on a "Cost Analysis and Rate Setting Manual for Animal Resource Facilities." In previous fiscal years we became aware that animal resources in many institutions were in financial difficulty. As a result we initiated a joint effort with the Business Officers Group of the Association of American Medical Colleges to develop a manual on cost analysis and rate setting for animal resource facilities. The manual was field tested in the summer of 1973 and subsequently revised and published. The manual will facilitate cost analysis in animal resource facilities, and this will lead to better cost control, management, and establishment of rates that will provide sufficient income for animal resource facilities. Much interest was expressed in the manual even prior to its publication. It is our intention that the manual be the basis for informing and educating investigators and sponsors of research that the full animal care costs should be supported by funding agencies through fees charged to users.

Another administrative activity this year has been a program evaluation of diagnostic laboratories. This activity is being carried out by a contract with the University of Missouri. The contract was awarded late in FY 1973 and calls for the development of a methodology to measure costs and benefits of the various diagnostic laboratory activities. When we started this project, we recognized we were dealing with an area that is hard to measure objectively; but as a result of recent meetings with (and reports from) the contractor, we are encouraged that a meaningful and workable system will be developed.

TABLE I - Primate Research Centers Program Applications, FY 1974

Type	<u>Number</u> <u>Received</u>	<u>Amount</u> <u>Requested*</u>	<u>Number</u> <u>Approved</u>	<u>Amount</u> <u>Approved*</u>	<u>Number</u> <u>Funded</u>	<u>Amount</u> <u>Funded**</u>
New	1	335,864	-	-	-	-
Renewal	1	1,606,242	1	1,484,092	1	1,492,367
Supplemental	2	134,894	2	115,418	3	302,709 ^{1/}
Continuation	6	12,109,893	6	10,721,537	6	9,696,924
Totals	10	14,186,893	9	12,321,047	10	11,492,000 ^{1/}

*Direct Costs Only

**Includes Indirect Costs

^{1/}Includes 2 prior approvals funded at \$260,000 from FY 1973 Impounded Funds.TABLE II - Laboratory Animal Sciences Program Applications, FY 1974

Type	<u>Number</u> <u>Received</u>	<u>Amount</u> <u>Requested</u>	<u>Number</u> <u>Approved</u>	<u>Amount</u> <u>Approved*</u>	<u>Number</u> <u>Funded</u>	<u>Amount</u> <u>Funded**</u>
New	36	2,960,327	19	1,070,911	42	3,384,955 ^{2/}
Renewal	15	1,421,146	8	431,134	8	662,230 ^{3/}
Supplemental	2	52,532	1	1,244	5	120,049 ^{4/}
Continuation	43	2,625,853	43	2,040,362	42	2,203,766
Totals	96	7,059,858	71	3,543,651	97	6,371,000

*Direct Costs Only

**Includes Indirect Costs

^{2/}Includes: 19 Prior Approvals funded at \$1,679,150
5 Prior Approvals funded at \$583,000 from FY 1973 Impounded Funds
18 FY 1974 Approvals funded at \$1,122,805

^{3/}Includes: 2 Prior Approvals funded at \$159,301
6 FY 1974 Approvals funded at \$502,929

^{4/}Includes: 1 FY 1974 Approval funded at \$1,493
4 Staff Supplements funded at \$118,556

TABLE III - Training Grant Applications in Laboratory Animal Medicine, FY 1974

Type	<u>Number</u> <u>Received</u>	<u>Amount</u> <u>Requested</u>	<u>Number</u> <u>Approved</u>	<u>Amount</u> <u>Approved*</u>	<u>Number</u> <u>Funded</u>	<u>Amount</u> <u>Funded**</u>
New	-	-	-	-	-	-
Renewal	-	-	-	-	-	-
Supplemental	2	49,749	2	49,749	9	194,713 ^{5/}
Continuation	6	449,880	6	387,979	6	242,287
Totals	8	499,629	8	437,728	15	437,000

*Direct Costs Only

**Includes Indirect Costs

^{5/}Includes: 7 Staff Supplements at \$141,000 funded from FY 1973 Impounded Funds
2 FY 1974 Approvals funded at \$53,713

TABLE IV - Fellowship Applications in Laboratory Animal Science, FY 1974

<u>Type</u>	<u>Number Received</u>	<u>Number Approved</u>	<u>Number Funded</u>	<u>Amount Funded</u>
New	10	6	-	145,300
Renewal	-	-	-	-
Supplemental	-	-	-	-
Continuation	<u>6</u>	<u>6</u>	<u>6</u>	<u>51,700</u>
Totals	16	12	6	197,000

TABLE V - Laboratory Animal Sciences Program Resource and Research Grants,
Project Distribution FY 1973 and FY 1974

<u>Project Type</u>	<u>No. Projects</u>	<u>Amt. in \$1,000's</u>	<u>No. Projects</u>	<u>Amt. in \$1,000's</u>
Basic Improvement	28	2,313	46	3,229 ^{1/}
Special Colonies & Models	20	1,141	22	1,250
Primate Resources	5	342	1	25
Resource Research	8	593	10	591
Diagnostic Laboratories	16	1,026	13	940
Reference & Information	<u>4</u>	<u>285</u>	<u>4</u>	<u>336</u>
Totals	81	5,700	96	6,371

TABLE VI - Laboratory Animal Sciences Program, Research Utilization of
Selected Animal Resource Colonies, FY 1974

<u>Colonies</u>	<u>No. NIH Grants</u>	<u>Dollar Amt. of NIH Grants in \$1,000's</u>	<u>No. Other Projects</u>	<u>Dollar Amt. Of Other Projects in \$1,000's</u>
Primate Resources	5	95	27	1,396 ^{2/}
Other Special Colonies	<u>11</u>	<u>55</u>	<u>39</u>	<u>750</u>
Totals	16	150	66	2,146

^{1/}Includes 5 projects (\$583,000) awarded from FY 1973 impounded funds

^{2/}Four of five projects completed support in FY 1974.

Fiscal Year 1974 Annual Report
Biotechnology Resources Branch
Division of Research Resources

MOST BIOMEDICAL RESEARCH INSTITUTIONS ARE "HAVE-NOTS" IN MOST AREAS OF BIOTECHNOLOGY!

- True?..... Yes, if one believes that every scientist who merits NIH support also deserves to have state-of-the-art research tools reasonably available.
- Critical?..... Absolutely, if one acknowledges that the vigor and success of modern biomedical science would be short-lived without its supporting tools and methodologies.
- Inevitable?..... Probably, at least insofar as biomedical research institutions choose or are forced to be exclusively inner-directed in attempting to fill their biotechnology needs.
- Immutable?..... No, not if NIH and the biomedical research community can effect successfully the sharing of highly specialized biotechnology resources across institutional lines.

The foregoing questions are the principal issues facing the Biotechnology Resources Branch (BRB). The answers reflect the present views of BRB staff and advisors. The following paragraphs review briefly some activities in FY 1974 -- and some prospects for FY 1975 and beyond -- which bear on these issues and answers.

BACKGROUND

The Biotechnology Resource is a vehicle through which the physical sciences, mathematics, and engineering are interfaced to biology and medicine. Such a resource combines expensive equipment, complex methodologies, and scarce expertise to facilitate the solution of important medical problems. A continuous effort to meet program goals is maintained within each resource by (1) providing services to the biomedical research community; (2) engaging in collaborative research arrangements with appropriate scientists; (3) engaging in core research and development designed to provide new technological opportunities for the research community and/or increase the usefulness of existing technology; and (4) providing training opportunities to the user community so that they can better understand the technology and apply it more effectively to their own research problems.

During the past few years it has become increasingly apparent that even some of the most distinguished biomedical research institutions throughout the country are unable to provide their member scientists with either up-to-date, health-relevant, research tools or the opportunity to collaborate with innovative experts at the technology/medicine interface. Accordingly, a concerted effort in Biotechnology Resource Sharing was initiated and promoted

during FY 1974 and will continue for the foreseeable future. The objective is to effect a more nearly equitable distribution of highly specialized research support capabilities in the nation, including especially those institutions having limited biotechnology capabilities but strong biomedical research programs and compelling biotechnology needs.

STATE OF THE PROGRAM

BASIC DATA

The variety of supported Biotechnology Resources and the diversity of assistance they provide the research community are shown by the following classification of the 55 grants and five contracts active during FY 1974.

- 23 computer resource grants
 - 2 resource-related projects in computer science
- 16 biomolecular characterization resource grants
- 6 biomedical image and image processing resource grants
- 1 resource-related project in biomedical image and image processing
- 7 biomedical engineering and other resource grants
- 1 electron microscopy services contract
- 4 clinical research data management and analysis developmental contracts

The aggregate annual expenditure level for these activities is approximately \$11 million. A listing of the BRB sponsored activities active during FY 1974 is given in Table I. A brief description of each Resource's capabilities, highlighted with an example of its application, is included in Table II. The interaction of the Biotechnology Resources Program with other NIH programs is shown in Table III.

It is particularly interesting to view the Biotechnology Resources Program in historical perspective. In 1967, for example, 61 resources were supported at a cost of \$12.2 million. These resources fell into the following categories:

- 48 computer resources
- 10 biochemistry instrumentation resources
- 3 biological materials resources

Both the numbers and the substantive nature of each type of resource have changed greatly during the intervening years, especially in the computer resource category. Compared to the 28 batch-processing or off-line, general-purpose computer installations in 1967, the Program had only one resource of this type in 1974. Whereas in 1967 the average annual award for a computer resource was about \$174,000, it was approximately \$418,000 in 1974. There seems to be little doubt that the ever more sophisticated computational needs of biomedical scientists are requiring highly specialized resources and not general-purpose ones.

TABLE I

BRB-SPONSORED ACTIVITIES DURING FY 1974
AS OF MAY 31, 1974

<u>Number</u>	<u>Principal Investigator</u>	<u>Institution</u>	<u>Title</u>	<u>FY 1974</u>	<u>Cumulative Awards</u>
RR-3-13	Wilfrid J. Dixon, Ph.D.	University of California, Los Angeles, California	Health Sciences Computer Resource	\$1,654,197	\$17,900,444
RR-7-11	Earl H. Wood, M.D.	Mayo Foundation, Rochester, Minnesota	Computer Processing in Biomedical Systems	488,878	4,322,522
RR-11-11	David D. Mason, Ph.D.	North Carolina State University, Raleigh, North Carolina	Computer Use in the Health Sciences	a/	1,257,829
RR-12-12	Homer R. Warner, M.D.	University of Utah, Salt Lake City, Utah	Biomedical Engineering Resource	285,066	2,394,958
RR-15-12	Martin Pring, Ph.D.	University of Pennsylvania, Philadelphia, Pennsylvania	Medical School Computer Facility	165,409	3,407,717
RR-16-10S1	S. James Kilpatrick, Jr., Ph.D.	Medical College of Virginia, Richmond, Virginia	Support of Scientific Computation Laboratory	a/	671,530
RR-117-11	William A. Clark, Ph.D.	American Type Culture Collection, Rockville, Maryland	Preservation of the American Type Culture Collection	a/	2,116,416
RR-145-10	Josiah Macy, Jr., Ph.D.	University of Alabama Medical Center, Birmingham, Alabama	Use of Electronic Computers in Health Research	a/	2,260,950

<u>Number</u>	<u>Principal Investigator</u>	<u>Institution</u>	<u>Title</u>	<u>FY 1974</u>	<u>Cumulative Awards</u>
RR-241-07S1	John J. Osborn, M.D.	Institute of Medical Sciences, San Francisco, California	Development of a Biomedical Research Data Facility	a/	\$ 1,598,333
RR-249-09	William S. Rhode, Ph.D.	University of Wisconsin, Madison, Wisconsin	Support of Laboratory Resources	\$ 274,560	2,009,716
RR-259-07	Allan H. Levy, M.D.	Baylor College of Medicine, Houston, Texas	Computational Research Center Program	170,045	2,234,581
RR-267-09	Eugene Ackerman, Ph.D.	University of Minnesota, Minneapolis, Minnesota	Health Computer Resource	299,040	2,655,946
RR-273-09	Richard Abrams, Ph.D.	University of Pittsburgh, Pittsburgh, Pennsylvania	Mass Spectrometric Facility for Biomedical Studies	53,562	443,045
RR-276-09	Ivan R. Neilsen, Ph.D.	Loma Linda University, Loma Linda, California	Development of Biomedical Computation Facility	108,869	960,228
RR-291-09	Jack Lubowsky, Ph.D.	SUNY--Downstate Medical Center, Brooklyn, New York	Biomathematical Computer Research Center	62,417	1,408,892
RR-292-09	Aksel A. Bothner-By, Ph.D.	Mellon-Pittsburgh-Carnegie Corporation, Pittsburgh, Pennsylvania	NMR Facility for Biomedical Studies	104,602	1,112,305
RR-311-06S1	Joshua Lederberg, Ph.D.	Stanford University, Stanford, California	Advanced Computer for Medical Research (ACME)	a/	4,135,308

<u>Number</u>	<u>Principal Investigator</u>	<u>Institution</u>	<u>Title</u>	<u>FY 1974</u>	<u>Cumulative Awards</u>
RR-317-07	Klaus Biemann, Ph.D.	Massachusetts Institute of Technology, Cambridge, Massachusetts	Mass Spectrometry Facility for Biomedical Research	\$ 139,596	\$ 1,400,692
RR-326-08	Cyril L. Comar, Ph.D.	Cornell University, Ithaca, New York	Computer Research Resources	65,742	588,047
RR-330-07	David Rosenthal, Ph.D.	Research Triangle Institute, Research Triangle Park, North Carolina	Mass Spectrometry Center for Research Triangle Region	103,495	705,302
RR-346-05	Henry G. Mautner, Ph.D.	Tufts University, Boston, Massachusetts	New England Enzyme Center	a/	551,606
RR-353-06	William J. Mueller, BSE	SUNY--Upstate Medical Center, Syracuse, New York	Research Data Processing Center	a/	787,052
RR-355-08	Martin F. Semmelhack, Ph.D.	Cornell University, Ithaca, New York	High Resolution Mass Spectrometer Facility	48,060	525,682
RR-356-08	Seymour R. Lipsky, M.D.	Yale University, New Haven, Connecticut	Continuation of Physical Sciences Instrument Facility	209,632	1,306,855
RR-370-04S2	Herbert M. Teager, Sc.D.	University Hospital, Boston, Massachusetts	Medical Computer Resource	a/	541,394
RR-374-07	Theodore H. Kehl, Ph.D.	University of Washington, Seattle, Washington	Support for Physiology and Biophysics Computer	178,412	883,832
RR-396-07	Jerome R. Cox, Jr., Sc.D.	Washington University St. Louis, Missouri	Computer Systems Laboratory-Biomedical Computing Laboratory	1,303,782	8,086,629

<u>Number</u>	<u>Principal Investigator</u>	<u>Institution</u>	<u>Title</u>	<u>FY 1974</u>	<u>Cumulative Awards</u>
RR-442-05	Cyrus Levinthal, Ph.D.	Columbia University, New York, New York	Computer Resource for Image Processing and Displays	\$ 219,562	\$ 1,039,163
RR-443-06	Robert Nathan, Ph.D.	California Institute of Technology, Pasadena, California	A Computer Resource for Pictorial Data Processing	320,761	3,153,897
RR-480-06	Charles C. Sweeley, Ph.D.	Michigan State University, East Lansing, Michigan	Support of Michigan State Mass Spectrometer Facility	81,582	523,848
RR-542-04	Mildred Cohn, Ph.D.	University of Pennsylvania, Philadelphia, Pennsylvania	220 MC NMR Spectrometer Facility	105,609	559,525
RR-570-0351 & -04	Hans Ris, Ph.D.	University of Wisconsin, Madison, Wisconsin	Electron Microscope Facility for Biomedical Research	76,458	923,905
RR-574-03	David M. Grant, Ph.D.	University of Utah, Salt Lake City, Utah	Regional Research Facility in NMR	98,016	380,076
RR-576-03	Harry Prystowsky, M.D.	The Pennsylvania State University, Hershey, Pennsylvania	Biomedical Computing Resource	140,282	424,622
RR-578-0451	Robert Langridge, Ph.D.	Princeton University, Princeton, New Jersey	Special Research Resource for Biomolecular Graphics	87,119	785,741
RR-592-04	Keith R. Porter, Ph.D.	University of Colorado, Boulder, Colorado	High Voltage Electron Microscopy of Biological Systems	192,290	1,113,254

<u>Number</u>	<u>Principal Investigator</u>	<u>Institution</u>	<u>Title</u>	<u>FY 1974</u>	<u>Cumulative Awards</u>
RR-612-04	Carl Djerassi, Ph.D.	Stanford University, Stanford, California	Resource-Related Research Computers and Chemistry	\$ 505,947	\$ 1,314,215
RR-636-02	Arthur P. Grollman, M.D.	Albert Einstein College of Medicine, Bronx, New York	Biotechnology Resource for NMR Studies of Bio-molecules	46,238	269,172
RR-639-01A2	Jay A. Glasel, Ph.D.	University of Connecticut Health Center, Hartford, Connecticut	A New England Area NMR Research Resource	162,222	162,222
RR-643-03	Saul Amarel, D.E.	Rutgers University, New Brunswick, New Jersey	Biotechnology Resource: Computers in Biomedicine	225,584	590,697
RR-657-01A1	Alfred P. Wolf, Ph.D.	Associated Universities, Inc., Brookhaven National Laboratory, Upton, New York	A Program in Support of Nuclear Medicine	237,960	237,960
RR-665-01	Rodger L. Foltz, Ph.D.	Battelle Memorial Institute, Columbus, Ohio	Regional Medical Mass Spectrometry Resource	87,076	87,076
RR-667-02	Harold W. Shipton, C.E.	University of Iowa, Iowa City, Iowa	A Biomedical Computer Terminal System	8,220	51,530
RR-679-02	Clifford A. Barger, M.D.	Harvard Medical School, Boston, Massachusetts	Biotechnology Resource in Electron-probe Microanalysis	158,678	297,076
RR-708-01	Nathan O. Kaplan, Ph.D.	University of California, SD., La Jolla, California	Special Resource for NMR and Mass Spectrometry	306,081	306,081

<u>Number</u>	<u>Principal Investigator</u>	<u>Institution</u>	<u>Title</u>	<u>FY 1974</u>	<u>Cumulative Awards</u>
RR-711-02	Oleg Jardetzky, M.D.	Stanford University School of Medicine, Stanford, California	High Frequency NMR Biotechnology Resource	\$ 57,490	\$ 188,479
RR-715-02	Elliott N. Shaw, Ph.D.	Associated Universities, Inc., Upton, New York	Electron Microscope Facility	75,510	162,240
RR-716-07	Harold W. Shipton, C.Eng.	University of Iowa, Iowa City, Iowa	A Bioengineering Resource Facility	231,711	247,931
RR-719-01 ALS1	A. L. Burlingame, Ph.D.	University of California, Berkeley, California	Biomedical Clinical Mass Spectrometry Resource	14,772	189,203
RR-734-01	Donald F. Parsons, M.D.	New York State Dept. of Health, Health Research, Inc., Albany, New York	Emulsions and Image Intensifier for the HVEM	128,153	128,153
RR-737-01	Joseph Kraut, Ph.D.	University of California, La Jolla, California	Implementation of a Laboratory Automation System	129,937	322,039
RR-739-01	Milton Helpert, M.D.	New York University, New York, New York	The Institute of Forensic Medicine as a Research Resource	a/	81,499
RR-735-01	Joshua Lederberg, Ph.D.	Stanford University, Stanford, California	S U Medical Experi- mental Computing Facility (SUMEX)	1,326,626	1,326,626
RR-857-01A1	Wen H. Ko, Ph.D.	Case Western Reserve University, Cleveland, Ohio	Biomedical Electronics Resource	433,318	433,318

Number	Principal Investigator	Institution	Title	FY 1974		Cumulative Awards
				\$	\$	
RR-862-01	Frank H. Field, Ph.D.	Rockefeller University, New York, New York	A Mass Spectrometric Bio-technology Resource	80,434	\$ 80,434	\$ 80,434

a/ Active during FY 1974 but received no FY 1974 funds.

CONTRACTS

NIH-70-4136	Robert M. Fisher, Ph.D.	U.S. Steel Engineers and Consultants, Inc., A Subsidiary of U.S. Steel Corporation, Pittsburgh, Pennsylvania	Access health scientists to the high voltage electron microscope located in the Edgar E. Bain Laboratory for Fundamental Research, Monroeville, Pa.	40,000	215,000
NIH-72-2098	Arthur W. Nunnery, M.D.	University of Oklahoma, Oklahoma City, Oklahoma	Development of a Clinical Research Data Management and Analysis Role for Computers	35,884	93,761
NIH-72-2102	T. G. Christopher, M.D.	University of Washington, Seattle, Washington	"	11,431	45,118
NIH-72-2104	H. K. Thompson, Jr., M.D.	Baylor College of Medicine, Houston, Texas	"	40,771	119,536
NIH-72-2106	Gabriel F. Groner, Ph.D.	The Rand Corporation, Santa Monica, California	"	171,460	406,451

TABLE II
RESOURCE CHARACTERIZATIONS

Computers

<u>Grant No.</u>	<u>Capability</u>	<u>Illustrative Applications</u>
RR-03-13	Batch processing, timeshare, and graphics	Biostatistical research; modelling cell cycle dynamics.
RR-07-11	Image processing and analysis	Non-invasive monitoring of cardiac function via roentgen video densitometry.
RR-11-11	Remote job entry to central computer	Biostatistical research; genetic modelling.
RR-15-12	Time sharing and batch processing	Biochemical kinetics modelling.
RR-16-10S1	Remote job entry to institution computer	Biostatistical research.
RR-145-10	Experiments hardwired to mini-computer which is hardwired to resource computer	On-line real-time data acquisition in cardiology and neurophysiology.
RR-241-07S1	Patient monitoring	Clinical research in cardio-pulmonary pathophysiology.
RR-249-09	Stand-alone minicomputers	On-line real-time control of neurophysiology experiments.
RR-259-07	Batch processing and tele-processing	Patient record management.
RR-267-09	Batch processing and time-sharing	EKG analysis.
RR-276-09	Dedicated systems and time-sharing	Computer assisted pulmonary function testing.
RR-291-09	Batch processing or dedicated digital analog system	Biomathematical modelling.
RR-311-06S1	Hardwired analog terminals and remote access timesharing	Acquisition and analysis of spectrometry data.

Computers (continued)

<u>Grant No.</u>	<u>Capability</u>	<u>Illustrative Applications</u>
RR-326-08	On-line interactive laboratory computing	Acquisition and processing of neurophysiology data.
RR-353-06	Data communication, batch processing	Hospital record management.
RR-370-04S2	Computer-based facilities for biomedical research	Real-time analysis of expired gas.
RR-374-07	Experiments hardwired to resource computers plus time-sharing.	On-line control and analysis of physiology experiments.
RR-396-07	Dedicated computers and macro-module systems	Cardiac rhythm monitoring; biomolecular modelling.
RR-576-03	Remote job entry to institution's computers; stand-alone minicomputer.	On-line real-time control of biomolecular characterization devices.
RR-578-04S1	Stand alone medium computer with graphics	Biomolecular modelling and computer-assisted design of organic synthesis.
RR-643-03	Access to timesharing systems	Application of artificial intelligence to clinical decision making.
RR-667-02	Terminal system design and fabrication	VHF short-range interactive digital computer communication.
RR-757-02	Computer-based automated laboratory systems	Image processing, on-line acquisition and processing of X-ray crystallography data.
RR-785-01A1S1	Remote access through computer networks	Applications of artificial intelligence in biology and medicine.

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TABLE II

RESOURCE CHARACTERIZATIONS

Biomolecular Characterization

<u>Grant No.</u>	<u>Capability</u>	<u>Illustrative Applications</u>
RR-273-09	Gas chromatography/low resolution, mass spectrometry/gas flow proportional counter	Metabolic profiles.
RR-292-09	High-frequency NMR, Multi-nuclear capability	Structure and function of hemoglobins and other molecules.
RR-317-07	Mass spectrometry-High resolution, gas chromatography/mass spectrometry, chemical ionization	Drug identification, Structure determination of unknown biomaterials.
RR-330-07	Mass spectrometry-High resolution, gas chromatography/mass spectrometry	Structure determination of potential anti-tumor drugs.
RR-355-08	Mass Spectrometry-High resolution, gas chromatography/low resolution	Structure determination of antibiotics.
RR-356-08	Mass spectrometry-High resolution, low resolution, NMR-Carbon-13, Proton, High performance chromatography	Separation and detection of nucleosides.
RR-480-06	Mass spectrometry-High resolution, gas chromatography/mass spectrometry, field desorption mass spectrometry	Structure determination. Lipids of biomedical importance.
RR-542-04	High-frequency NMR	Enzyme/substrate interaction mechanisms.
RR-574-03	NMR-multinuclear capability	Carbon-13 labeled macromolecules.
RR-612-04-05	Resource related research Mass Spectrometry	Application of artificial intelligence to mass spectrometry.
RR-636-02	NMR-multinuclear capability	Structure and function of peptide hormones

Biomolecular Characterization (continued)

<u>Grant No.</u>	<u>Capability</u>	<u>Illustrative Applications</u>
RR-639-01A2	NMR-Proton, Carbon-13	Carbon-13 studies of nucleoside bases.
RR-665-01	Mass spectrometry-High resolution, gas chromatography/low resolution, chemical ionization	Structure identification of natural products.
RR-708-01	Mass spectrometry, gas chromatography/low resolution, NMR-220MH _z	Metabolic studies, Structure and function of biomolecules using stable isotopes.
RR-711-02	NMR - 360MH _z	Structure and function of macromolecules.
RR-719-01A1S1	Mass spectrometry-High resolution, gas chromatography/high resolution, low resolution	Application of mass spectrometric techniques to clinical problems.
RR-862	Mass spectrometry-chemical ionization	Application of mass spectrometry to medical problems.

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TABLE II

RESOURCE CHARACTERIZATIONS

Biomedical Image and Image Processing

<u>Grant No.</u>	<u>Capability</u>	<u>Illustrative Applications</u>
RR-442-05	Image processing and displays	Neuroanatomical modelling.
RR-443-06	Image processing	Electronmicrographs and medical images.
RR-570-03S1-04	One-million volt electron microscope	Structure and function of chromosomes.
RR-592-04	One-million volt electron microscope	Structure and function of the nucleolus.
RR-679-02	Electron microprobe	Histochemistry - quantitative analysis of renal cell composition.
RR-715-02	Scanning electron microscope	Under development.

TABLE II

RESOURCE CHARACTERIZATIONS

Biomedical Engineering and Others

<u>Grant No.</u>	<u>Capability</u>	<u>Illustrative Applications</u>
RR-12-12	Activities hardwired to resource computer	Patient monitoring; medical record management.
RR-117-11	Methods of characterization preservation and distribution	Systematic collections of microorganisms, viruses, cell lines, and other pertinent organisms.
RR-346-05	Protein isolation	Large scale preparation of enzymes and microbial cells.
RR-716-07	On-line real-time integration methods; on-line real-time display	Interfacing of laboratory instruments to computers; acquisition of electrophysiological and other biological data under computer control.
RR-759-01	Serology, toxicology, histology	Forensic pathology.
RR-857-01A1	Microelectronics fabrication, packaging, and evaluation capabilities	Microelectronics devices for biological and clinical research.

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TABLE III

NUMBER & DOLLAR AMOUNT, BY NIH INSTITUTE, OF PROJECTS
RECEIVING TECHNOLOGICAL SUPPORT FROM A SAMPLE OF 23 OF THE 51

BIOTECHNOLOGY RESOURCES

ACTIVE DURING FY 1973

Institute	Number of Projects	Dollar Value of Project (in millions)
Allergy and Infectious Diseases	12	\$ 1
Arthritis, Metabolism and Digestive Diseases	36	2.7
Cancer	34	3.5
Child Health and Human Development	31	2.8
Dental Research	4	1.4
Environmental Health Sciences	4	.2
Eye	8	.3
General Medical Sciences	68	8.1
Heart and Lung	55	4.9
Neurological Diseases and Stroke	43	3.5
National Library of Medicine	3	.2
Health Services and Mental Health Administration	54	6.8
Contracts	25	7.4
	<u>377</u>	\$ <u>42.8</u>

Projected Totals for all 51 Active Grants

Number = 836

Value = \$ 95 million

Rapid and far-reaching change is not limited to the computer resource category. For example, as the requisite talent becomes available to manage mass spectrometers in a variety of biomedical settings, there is a strong trend toward the use of these instruments in clinical investigation, such as the study of metabolic errors in infants. It is also of interest to note that, unlike even a few years ago, all of the biochemistry instrumentation resources now contain a dedicated computer for reduction of data to a manageable form. Similarly, almost exclusively as a result of efforts by the Biotechnology Resources Program in the past several years, high voltage (i.e., one-million volt) electron microscopy services have become a reality in the United States and are now being applied for such purposes as obtaining stereo micrographs of thick-sectioned biological material and examining the surfaces and contacts of intact wet cells in a hydration chamber.

The eight new awards made by the Biotechnology Resources Program during Fiscal Year 1974 demonstrate the continuing diversification and specialization of supported activities. These new resources include a computer resource, four biomolecular characterization resources, two biomedical engineering resources, and a resource-related research project in high voltage electron microscopy.

BIOTECHNOLOGY RESOURCE SHARING

The succeeding sections will describe representative biotechnology resource activities in several areas. It is obvious that these biomedical research activities are of great value to their respective research communities. It is also apparent that these research communities are especially fortunate in having these excellent opportunities immediately available.

Because these highly specialized resources are both expensive and dependent on critical assemblies of scarce talent, only a few medical research centers having needs for them can be accommodated by the BRB, using traditional program support mechanisms, within present and foreseeable funding constraints.

Moreover, these specialized resources usually must have great capacity in order to function effectively. At the same time such great capacity may exceed the needs of a single institution, yet could be of even greater value with specific supplementation.

The logical solution to these problems of high costs, scarce talents, needs for broad and versatile resource support, and inter-institutional collaboration, lies in linking and sharing resources.

Because of the varied natures of sharable resources, specific appropriate administrative arrangements are needed. Some biotechnology resources, such as computers which can be linked by telecommunication networks, are readily adapted to the shared mode. Others, e.g., the HVEM resources, presently require that the investigator and the problem be brought to the resource facility, under suitable arrangements assuring effective management, participation of qualified researchers, needed training, and ongoing evaluation of effectiveness as a shared resource.

Assembly of related but dissimilar biotechnology resources into shared networks offers the advantage of pooling diverse talents and instrument capabilities to produce levels of capability superior to those of any component.

This pooling effect has special benefits for those investigators and institutions with potential, but who for lack of opportunity have inadequate training and experience in the exacting skilled fields encompassed. Sharing of resources therefore offers opportunities for disadvantaged institutions and isolated investigators. However, the linking of institutions and investigators of grossly dissimilar levels of sophistication poses new problems of program management to assure equitable involvement of the "have" and "have not" components in shared resource systems. Both the review and the ongoing management by NIH staff must enter a new dimension.

The benefits of shared biotechnology resources are obvious. These include: (1) the support of a larger and more varied body of investigators and problems, (2) fuller utilization of expensive instrumentation, (3) increased collaboration between investigators in different institutions who have research interests in common, and (4) the increase in numbers and quality of researchers and institutions able to benefit from sophisticated biotechnology approaches to their biomedical activities.

Although shared biotechnology resource programs are still in comparative infancy, the potential for expansion is impressive. The experience gained in developing and managing these arrays may well establish patterns of wide applicability in biomedical research.

COMPUTER RESOURCES

CLINICAL DECISION MAKING IN GLAUCOMA

Research on the management of medical knowledge relevant to glaucoma diagnosis and therapy at Rutgers University and Mt. Sinai School of Medicine is now making clinically significant contributions. A conceptual model of how this knowledge is organized for computer-based problem solving is an iceberg: the visible portion is the set of observed signs and symptoms; at the water line are descriptions of disease states appropriate to the specific patient; and under the water are found the detailed normal and pathophysiological models containing most of what is known about glaucoma-related ocular mechanisms and functions. This system is designed to trap inconsistent observations, to be restructured and rebased from new knowledge acquired from the experts in glaucoma as they interact with the system, to provide the rationale for each action recommended, to simulate how each of several glaucoma experts would handle a difficult case, and to provide advice on diagnosis and therapy through the stages of glaucoma. Linkages between experts at different institutions and the Rutgers group are being developed to broaden and deepen this effort and its impact.

At present the system contains about 80 causal states associated with glaucoma. This number seems to be approaching the optimum for an effective yet efficient clinical consultation tool for those dealing with this disease. Future work will strengthen the linkages between the disease state and the pathophysiological models and explore how knowledge of the disease and computer-predicted consequences of candidate therapeutic actions can be organized and presented in the most compact but comprehensive form.

SUMEX-AIM

During FY 1974 the BRB awarded funds for the creation of SUMEX, Stanford University Medical Experimental facility. This resource is the first and only such installation expressly devoted to research on Artificial Intelligence in Medicine (AIM). The SUMEX computer has 50 per cent of its capacity devoted to AIM activities within the Stanford University Medical School and the remaining 50 per cent of the capacity allocated to AIM activities throughout the country via computer networks. The initial SUMEX/AIM community includes mass spectrometry data interpretation studies at Stanford, the glaucoma activity at Rutgers University, and X-ray crystallography studies at the University of California at San Diego. National solicitation to identify additional qualified participants will be conducted early in FY 1975.

The intellectual ties among the SUMEX-AIM participants are expected to serve as a key element of the shared resource function. Benefits should accrue through exchange of ideas and techniques, and these interactions should lead to further strengthening biomedical research through collaboration both within the artificial intelligence community and between the computer scientists and their medical research counterparts.

AIM WORKSHOPS

Health researchers outside the SUMEX-AIM activity have expressed interest in learning more about these advanced computing techniques and their potential biomedical application. As a result, a series of AIM workshops are planned. These workshops are to be an arena where biomedical scientists with significant health research problems can interact with advanced computer scientists who are stimulated by the methodological challenges of the biomedical milieu. The Biotechnology Resource at Rutgers University will be the focus for these workshop activities.

CANDIDATE NEW TOOLS FOR PROGRAM MANAGEMENT

There have been many subjective indicators over the years suggesting that the BRB Program best serves the biomedical research community by encouraging the development and use of specialized computer resources rather than general-purpose ones. Therefore, it is important to assess the relative costs of specialization and generality. Measures of total costs to create both generalized and specialized computer centers have, interestingly enough, shown

little difference; and, in most cases, those computer systems especially developed for the research community are more vigorously utilized than general-purpose ones, i.e., utilization by the research community is much higher when their needs are addressed directly by the staff and system of a Biotechnology Resource.

Utilization of computer system capacity can be evaluated effectively by various metrics. The computer systems supported by the BRB Program have in common the mission to diffuse technology into health research. The proposed selection of talent and equipment to do this is reviewed in the beginning for each resource. The progress of the resource in serving qualified investigators can be examined by observing the ratio between this utilization and the size of the systems and applications programming staff. It is important that both systems and applications work be included in this analysis, for the more effectively the systems programmers bend the machine to serve man, the less need there is to provide applications programming support to the user community. After a resource has achieved mature and stable capabilities, strong effort is required to maintain a competitive edge with the constantly emerging new computer technology. The BRB diffusion metric (user hours/computer programming FTEs) is sensitive to these variations and strengths.

Cost measures also are central to this analysis. BRB interests in cost measures stem from the programmatic goal of having biomedical computer technology contribute optimally within the funds available. The strategy has been to create and nurture resources and then to see at least their routine service components sustained without further BRB funds. Costs obviously play an important role here, for if a resource is to become self-sustaining, it must be able to compete for computing dollars within its own environment. Thus, a cost measure such as total production time in hours per year divided by the average annual BRB award dollars per year gives a measure through the BRB-support stages. Average annual amounts are used to cover rental/purchase variations introduced by alternative procurement methods selected by the grantees. Total computer production time is the total core research and user time interacting directly with the computer as is indicated in the annual resource usage summaries, i.e., total man/machine interaction time.

When this cost measure and the above diffusion measure are graphed and examined together for a single resource, year-by-year changes show the development of that resource in time.

When the diffusion metric and cost metric are plotted for all computer resources (Figure I), a general separation of resources into highly successful and moderately successful operations is observed. Should this observation prove to be consistent in time, it can become a valuable management tool for this Program.

OBSERVATION ON RESOURCE
EFFECTIVENESS FROM FY'73-74 DATA

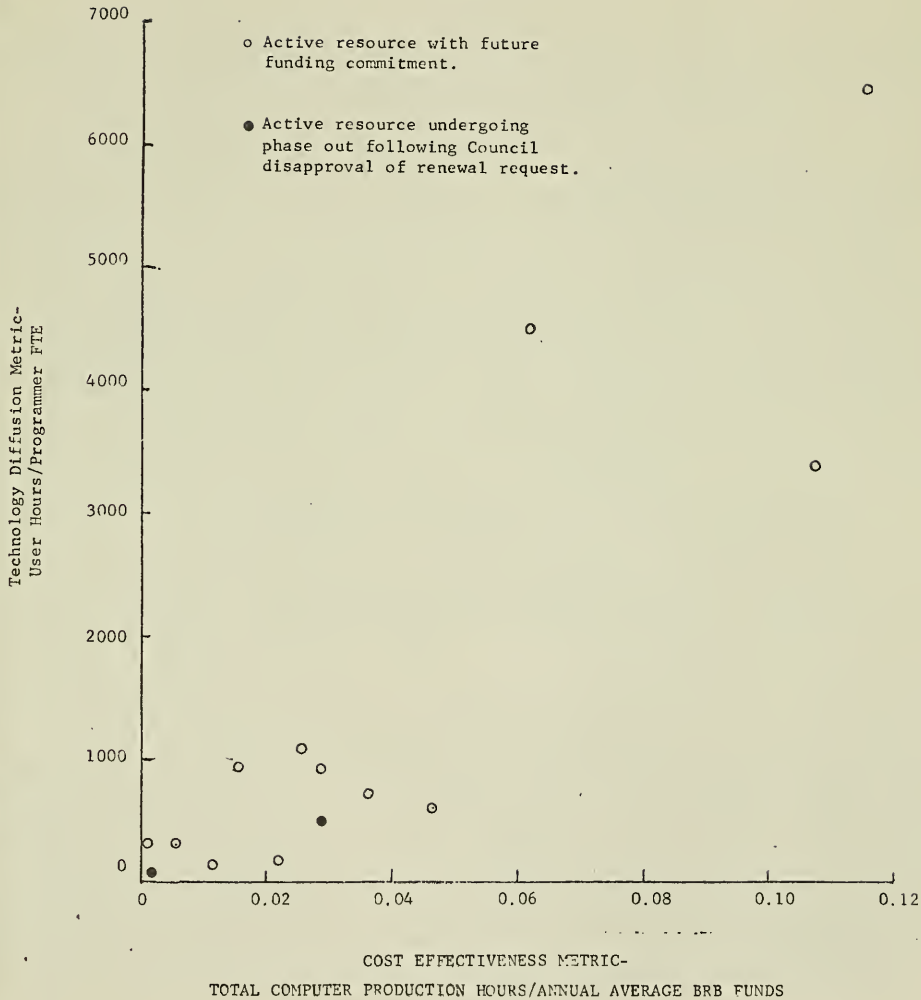


FIGURE I

When taken separately over the entire computer resource program, the cost measure shows the effectiveness in moving from batch-processing systems to specialized systems developed for specific research needs, as shown in the cost/effectiveness metric during the years 1968-1973.

<u>BRB Dollars Per</u>	<u>1968</u>	<u>1969</u>	<u>1970</u>	<u>1971</u>	<u>1972</u>	<u>1973</u>
<u>Computer Pro-</u> <u>duction Hour</u>	\$91/hr.	\$70/hr.	\$72/hr.	\$52/hr.	\$32/hr.	\$27/hr.

CLINFO

The CLINFO project is a scientific inquiry sponsored by the BRB and General Clinical Research Centers Branch. It is aimed at identifying and characterizing the information analytic tasks and the information flows in human clinical investigation and at developing methods for facilitating these tasks and flows. The first phase of the inquiry gathered information about and characterized the investigative processes, identified potential roles of computer technology in facilitating clinical research, and identified existing and potential systems to fill these roles.

CLINFO is currently being effected by a consortium comprised of clinical contractors at Baylor College of Medicine, the University of Oklahoma, and the University of Washington, information scientists at The Rand Corporation, and staff members of DRR. The clinical contractors have been contributing knowledge about clinical research, the information scientists have been contributing experience in computer technology and knowledge of information science, and DRR staff members have been providing overall direction.

The CLINFO project has thus far

- broadly characterized clinical research activities,
- identified research data management and analysis as major problems in clinical research,
- shown (through an extensive survey of clinical investigators) that these problems are widespread, and
- examined a number of existing systems that might alleviate these problems.

The present goal is to increase the quality and effectiveness of clinical research by developing an economical, readily accessible, widely usable computer system that, together with specially trained personnel, will help clinical investigators to collect, organize, store, retrieve, and analyze their research data. Past attempts to develop useful computer systems have often failed because development projects have been uncoordinated and inadequately staffed, because they have not had an adequate understanding of the hardware, software, and personnel requirements, and because they have not adequately tested the systems with a variety of users in a variety of situations. Plans for the next phase include a well staffed, well tested, evolutionary approach which will

- implement an initial prototype system;

- install copies of this system at the three clinical-investigator contractors' institutions where they will be used by several investigators during the course of their execution of approved protocols;
- investigate the use of the prototypes, and (as unobtrusively as possible) modify the systems functional characteristics to maximize their acceptability and utility to a broad variety of users;
- estimate the benefits and operating costs of the prototypes; and
- test the conclusions reached by installing a stable version of the system at and providing personnel to an additional clinical research center where there is no CLINFO contractor and by (passively) observing its use there.

Thus in the next three years the project is to develop a prototype clinical research data management and analysis system and test it with several clinical investigators at each of four sites, including one where there is no CLINFO contractor. The expected results are

- a tested, practical system which can continue to operate at the four sites and which can be duplicated and further distributed in a straightforward fashion;
- documentation of the requirements for, and benefits of, a system designed to have wide applicability;
- knowledge about how to introduce such systems into new institutions, how to promote their use, and how to assist and educate their users;
- information about the requirements for both on-site and centralized personnel to perform these functions;
- a dispersed, trained group of such personnel; and
- a number of newly uncovered problems whose solution could benefit clinical research.

BIOMOLECULAR CHARACTERIZATION RESOURCES

During FY 1974 the scope of the Biomolecular Characterization Resources Program was expanded to encompass a broader range of capabilities within the areas of mass spectrometry and nuclear magnetic resonance spectroscopy. As illustrated in Table II, each Resource is a unique complement to the total program.

For example, a significant impact has been made in the area of clinical mass spectrometry through the Biomolecular Characterization Resources Program. Although the technology has not reached the status of a routinely useable tool for the clinical chemistry laboratory, sufficient experience was gained during FY 1974 to encourage continued emphasis in this area.

At the Michigan State University Mass Spectrometry Facility computer-based techniques have been developed in combination with gas chromatography/mass spectrometry to allow rapid simultaneous identification and quantification of a large number of compounds in urine or other biological fluids as an aid to disease diagnosis and metabolic studies.

A unique and powerful tool, a combined gas chromatograph/mass spectrometer/gas flow proportional counter system, has been developed at the University of Pittsburgh's Mass Spectrometric Facility for Biomedical Research. This instrument makes it possible to separate the components present in an extract of cells or growth medium, identify them, quantitate each component, and assay their isotope content. From such information an accurate metabolic profile can be determined. The system is being applied to a model study designed to diagnose muscular dystrophy at the embryonic level. The availability of such prenatal information would be invaluable in helping to make a decision whether or not to terminate a pregnancy.

An important addition to the clinical mass spectrometry program resulted with funding of the Biomedical Clinical Mass Spectrometry Resource at the Space Sciences Laboratory, University of California, Berkeley. This Laboratory, originally financed through NASA, is making available to the clinical community extensive facilities and expertise assembled under the national space program. Of particular interest is the development of a combined gas chromatography/high resolution mass spectrometry system that should have numerous applications in the analysis of biological fluids containing minute quantities of unknown substances.

In the area of nuclear magnetic resonance spectroscopy, a 360 MHz₂ instrument, funded jointly with the National Science Foundation, was acquired by the High Frequency NMR Biotechnology Resource at the Stanford University Medical School and in the near future will be widely available to scientists with appropriate problems.

As part of the BRB commitment to resource sharing, steps have been initiated to develop a coordinated national effort in mass spectrometry and nuclear magnetic resonance spectroscopy. Each center is being encouraged to specialize according to expertise, primary fields of interest and experience, and hardware capability to maximize its effectiveness and impact on important medical problems. The BRB has undertaken the development of a Resource Directory for distribution to NIH grantees and contractors to aid them in identifying sources of highly specialized analytical support available through the program.

HIGH VOLTAGE ELECTRON MICROSCOPY RESOURCES

The High Voltage Electron Microscopy Resources at the University of Wisconsin and the University of Colorado -- and the contract with U.S. Steel Corporation to purchase time on their one-million volt electron microscope -- are another part of the shared resources program in BRB. These resources are national in scope and are available to qualified biomedical investigators throughout the country. Administrative mechanisms have been established to insure that the community of potential users outside the resources' institutions know about the

installations and of their opportunity to make application for their use. An ad hoc advisory group to BRB assists in the review of applications for beam time from these scientists, and BRB staff informs these applicants of the results of the review.

During the past year approximately 20 per cent of the microscopes' operating time at the Universities of Colorado and Wisconsin HVEM Resources was allocated to off-campus users. Time purchased by the BRB on the U.S. Steel million volt microscope is used completely by outside scientists. The Colorado and Wisconsin Resources are prepared to allocate up to 50 per cent of the operating time and associated technical assistance to outside users, as the demand from this group increases sufficiently to require this amount of time. If more microscope time is needed for local or outside users, these facilities can operate additional shifts.

During the past year considerable progress has been made in the Resources in developing applications of HVEM in biomedical research. The greater penetration and higher resolution gained by the use of the HVEM presents some important advantages to electron microscopists. Small cellular structures such as chromatin fibers, microtubules, microfilaments, and ribosomes are seen with clarity in thick sections at 1000 kv with spatial relationships between structures preserved. The ability to observe whole cells is proving important in studying the interaction of virus and cell. The probability of finding virus particles suspected to be present in small numbers is greatly enhanced when viewing thick sections and whole cells in the HVEM. Using thick sections for autoradiography experiments shortens the exposure times by a factor of 10 to 20. Grain densities that take months to form in the thin sections required in 100 kv microscopes are obtained in two to three days with thicker sections in the 1000 kv instrument. The reconstruction of three-dimensional structure and organization of intracellular systems from stereo images of thick sections in the HVEM is proving to be more accurate and less tedious than has been possible using serial thin sections. The ease with which thick sections can be cut and handled is another practical advantage of high voltage electron microscopy.

There is a need for better photographic emulsions for the HVEM. Emulsions presently available were developed for the lower voltage microscopes and are not as sensitive at one million volts. To meet this need BRB awarded the Roswell Park Memorial Institute a resource-related research project grant designed to develop more sensitive emulsions for the HVEM. The three BRB HVEM Resources will cooperate in testing and evaluating the emulsions developed by this grantee.

BIOMEDICAL ENGINEERING RESOURCES

A biotechnology resource specializing in microelectronics for health research was funded during this year. This resource is based upon an established program at Case Western Reserve University focused on strengthening biomedical engineering capabilities; the goal of the new resource is to interact with health scientists in ways that lead to new and improved capabilities of general applicability to health research and patient care. The role of the biomedical

engineer in this setting is to reduce the research overhead of medical scientists by providing ways to gain information which is attainable only with micro-electronics techniques.

This resource, through its past experience and present capabilities, provides a base to develop telemetry devices which can be

- implanted in the human body to study stress and strain of orthopedic appliances,
- implanted to monitor intercranial pressure, cerebral spinal fluid pressure, and pO_2 of neurosurgical patients and hydrocephalic children, and
- implanted for chronic monitoring of a patient's condition after organ transplant or other critical surgical procedures;

and implant stimulation devices which can effect

- pain suppression by stimulation in spinal cord or periphery,
- blood pressure control of hypertensive patients, and
- control of central nervous system functions.

Using the above devices, systems may be developed to operate an internal signal to control and study the regulation of body functions. Ameliorative steps such as providing a bypass for a damaged neural network is possible with a system of implanted sensors and stimulators.

The collaboration activities of this resource in the past have been with single collaborators on each research area. Extension to other collaborators is desirable to test the efficacy of the ideas in a number of research environments; it is important that the commonality of research needs met by the engineering product be determined and the number of sites for its potential diffusion be multiplied.

The opportunity to examine the processes of pursuing these goals through the resource mechanism is offered in this activity. Two measures of progress can be identified. Early in the resource's life progress may be measured by the strength and geographical range of the resource's collaborative activities. Later, successes may be evaluated in terms of the range and value of the resource's services that are subscribed to by outside users and the appearance and national diffusion of its "finished products" in the commercial marketplace.

RESOURCE SHARING - SUMMARY

The following tables display and summarize the nature, status, and projected future of shared resource programs. Shared biotechnology resources must meet the present four essential criteria for BRB resources and in addition must include inter-institutional collaboration in research, policy, and management activities. Presently active BRB shared resources are described above. Shared BRB resources under development or planning are listed in Table IV. Potential sharing of resources need not be limited to biotechnology. Table V suggests other DRR and NIH programs that might benefit from shared arrangements.

TABLE IV

SHARED BIOTECHNOLOGY RESOURCES UNDER DEVELOPMENT OR CONSIDERATION

Biomolecular characterization resources

High resolution mass spectroscopy
Nuclear magnetic resonance spectroscopy
X-ray crystallography
Activation analysis

Biomedical computer specialized resources

Modeling of biological processes
Molecular modeling
Image processing
Biomedical graphics
Biostatistics
Chemical-biological information-handling

Electron probe resources

Biomedical engineering resources

Diffusible products —————> computer instruments and sensors
Programmed console for radiation therapy
Clinical monitoring systems

TABLE V

OTHER POTENTIALLY SHAREABLE RESOURCES

Primate Centers

Animal Research Resource Development Centers

Clinical Research Centers

Pharmacology-Toxicology Centers

Dental Research Institutes

Environmental Health Centers

Sickle Cell Centers

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In the development and on-going management of shared resources several considerations must be kept in mind in addition to those that pertain to traditional research resource support programs. The preparation by applicants of requests for support of shared resources will need consultation and advice by staff to ensure that plans for inter-institutional sharing are described clearly. The peer merit review of proposals must include, in addition to the traditional considerations, evaluation of the need for and the feasibility of the proposed sharing arrangements.

The management of NIH-supported shared resources must take into account the increased complexity of multi-institutional relationships, geographical separation, and unequal sophistication of participants. This management must be a partnership among components, including an on-going role for the staff of the supporting agency.

The management must provide for

- equitable responsibilities and opportunities for all participants -- both suppliers and users of services,
- justified expansion of opportunities -- including training for inexperienced candidates needing to participate,
- equitable funding support among components,
- appropriate participation by funding agency, and
- on-going inter-institution management (broker function).

In planning and setting up national networks of shared resources, the need for subsequent evaluation of effectiveness must be recognized. This evaluation can be done most dependably if incorporated into the original design, so that records will reflect the basis for and consequences of decisions made. It will then be possible to make comparative measurements of relative effectiveness in terms of program and costs.

These considerations hopefully will evolve into an agenda for action insofar as further biotechnology resource sharing is concerned. But meaningful action on the agenda will take place only if both the letter and spirit of these concepts are embraced by leaders in the biomedical research community. BRB staff and advisors look forward to playing at least a small role in catalyzing the testing and elaboration of these concepts in the real world of biomedical science. There is little doubt that the key contributions of biotechnology resources toward fulfilling the NIH mission will be even more visible in the future than they have been in the past.

Fiscal Year 1974 Annual Report
Chemical/Biological Information-Handling Program
Division of Research Resources

Fiscal Year 1974 marked the continued maturation of the Chemical/Biological Information-Handling (CBIH) Program and its specialized computer resource called the PROPHET System. There was steady growth in all relevant parameters of PROPHET usage (i.e., number of users, diversity of applications, intensity of user/System interaction, and sophistication of user efforts). There also was steady elaboration of System capabilities by developers and users alike. This simultaneous evolution of both tool and usage produced operational problems to be solved, technological challenges to be met, and scientific opportunities to be seized. The following paragraphs summarize the events and issues which highlight the past year and promise further progress in the next.

BACKGROUND

THE CBIH PROGRAM

The CBIH Program, in keeping with the mission of the Division of Research Resources, NIH, is concerned with providing biomedical scientists with the research support capabilities they most need to pursue their investigations effectively. The focus specifically is on (a) designing and developing computer-based information-handling tools important to studies of chemical/biological interactions (a line of inquiry relevant to almost every major medical area); (b) making these tools available to the national scientific community in an easy-to-use and highly reliable form; and (c) collaborating with the users of these tools in order not only to refine and extend them but also to develop deeper insights into the investigative process itself. Particular emphasis is placed on questions of where and how computer technology and information science can catalyze the emergence of predictive capabilities regarding the interactions of chemical substances and living systems.

THE PROPHET SYSTEM

The heart of the CBIH Program is the PROPHET System, a computer resource specialized to meet the information-handling needs of individual laboratory and clinical investigators in the pharmacology/toxicology area. This resource is operated in such a way that its unique capabilities are available to qualified scientists on a national basis, irrespective of geographical location or institutional affiliation. A brief description of this research tool is included as an Appendix to this report.

SCIENTIFIC APPLICATIONS

As of this writing, the services of the PROPHET System are available principally to scientists at the five sites indicated in Figure 1. At each of these sites there is located an identical configuration of equipment--namely, graphic display device, hard copy unit, graphic input tablet, and telephone modem. In addition, scientists at two other institutions (Beth Israel Hospital in Boston, Mass., and Harbor View Hospital in Seattle, Wash.) make use of the System via more limited teletype-like terminals.

The scientific problems being investigated with the aid of PROPHET span the spectrum from quantum pharmacology to human clinical investigation and map onto interest areas of most major NIH components. Figure 2 is a listing of those user projects funded by NIH/NIMH. This listing shows that the PROPHET System is employed within the mainstream of research on chemical/biological interrelationships.

A particularly gratifying event in FY 1974 was the invitation to the CBIH Program to organize a two-hour session on the PROPHET project for the National Computer Conference (NCC). This meeting was an excellent opportunity to document in considerable detail in a widely read publication (the NCC Proceedings) both a characterization of the System and selected examples of the uses to which it is put. A description of the NCC Session on PROPHET is included as Figure 3. Reprints of the papers indicated are available on request.

Looking to the future, there is good reason to believe that PROPHET's positive impact on pharmacological science will continue. In addition to the present user groups, there are several other cadres of scientists whose proposed PROPHET uses already have been adjudged highly meritorious in national competition before peer review panels and who await a terminal and accoutrements. Within the constraints imposed by the System capacity and the number of contractor personnel engaged, the CBIH Program places its highest priority on accommodating as many of these prospective users as is consistent with the continuing provision of reliable research services and the orderly development of PROPHET's capabilities.

NEW CAPABILITIES AND FEATURES

The PROPHET users provide the refining fire for the evolving array of information-handling tools offered by the CBIH Program's major contractors (Bolt Beranek and Newman Inc. and First Data Corporation). The users also are the single most valuable source of critique and guidance as to which candidate new features merit development and in what form. Much effort has been and will continue to be expended toward making the PROPHET System user-driven.

The principal results of this user-driven design/development process in FY 1974 are summarized in Figure 4. The new data type SAMPLE and its associated procedures represent a quantum jump in terms of easy-to-use data analysis tools and furnish a standard interface to guide the continuing

PROPHET USERS AS OF JUNE 1974

1. Department of Pharmacology
School of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania
2. Harvard Medical Unit
Thorndike Memorial Laboratory
Boston City Hospital
Boston, Massachusetts
3. Department of Pharmacology
Mount Sinai School of Medicine
City University of New York
New York, N. Y.
4. Molecular Biophysics Department
Medical Foundation of Buffalo
Buffalo, New York
5. Research Institute on Alcoholism
New York State Department of
Mental Hygiene and
State University of New York at Buffalo
Buffalo, New York

Figure 1.

USER PROJECTS FUNDED BY NIH/NIMH

University of Pittsburgh:

MH-11682-07	Hallucinogenic drug action on somatosensory systems (primates)	G. Werner
AI-08192-06	A phenotypic resistance to tetracycline (bacteria)	R. H. Connamacher
NS-07923-06	Nervous control of urinary bladder and large bowel (cats)	W. C. DeGroat

Boston City Hospital (Harvard Medical Unit):

RR-00076-12	General clinical research center	F. H. Epstein
GM-19954-02	Factors inducing the abnormal metabolism of trauma	G. H. Clowes
GM-20630-01	New concepts in parenteral protein sparing therapy	G.L. Blackburn
ES-33332	Epidemiologic studies and chronic respiratory diseases	F. E. Speizer
AI-04716	Eosinophil functions	M. Litt
HL-5988-01	Clinical epidemiology of heart and lung disease	F. E. Speizer
HL-10539-08	Pathophysiology of the circulation	W. H. Abelmann
HL-15571-02	Water and electrolytes in health and disease	F. H. Epstein
HL-16237-01	Computer feedback study of cardiac muscle mechanics	O. H. Bing
AM-05060	Metabolism training program	D. A. Arky
AM-05413	Nutrition training program	C. S. Davidson
AM-08681	Diseases of the liver and portal circulation	W. V. McDermott, Jr.

(continued)

Figure 2.

Mount Sinai School of Medicine:

MH-17489-03	Psychopharmacologic activity -- quantum chemical study (rats)	J. P. Green
MH-25644	Psychopharmacological changes following brain damage	S. Glick

Medical Foundation of Buffalo:

AM-05619-05	Training Program in Endocrinology	H. Hauptman
AM-15051-03	Molecular structures of thyroactive compounds	H. Hauptman
CA-10906-07	Molecular structures of steroids	W. L. Duax
CA-13540-02	Cancer of the thyroid and its hormonal identity	E. M. Volpert
GM-19684-02	Ionophores, transport and membrane structure	W. L. Duax
HD-94945-04	Human development and estrogen biosynthesis	Y. Osawa
HL-15378-02	Ultrastructure of antihypertensive prostaglandins	J. Edmonds

Research Institute on Alcoholism:

Still in only its first year of operation, this Institute now receives the bulk of its research support from New York State. Several grant applications now are under review, however, by the NIH and other components of the DHEW.

Figure 2. (cont'd)

1974 NATIONAL COMPUTER CONFERENCE AND EXPOSITION

May 6-10, 1974

McCormack Place, Chicago

Session Description

Title: The PROPHET System: Computing in Pharmacology

Introduction	William F. Raub, Ph.D. National Institutes of Health
The Implementation of the PROPHET System	Paul A. Castleman Bolt Beranek and Newman Inc.
Applications of the PROPHET System in Correlating Crystallographic Structural Data with Biological Information	Charles M. Weeks, Ph.D. Medical Foundation of Buffalo
Applications of the PROPHET System in Molecular Pharmacology: Structure Activity Relationships in Monamine Oxidase Inhibitors	Carl L. Johnson, Ph.D. Mount Sinai School of Medicine
Applications of the PROPHET System in Human Clinical Investigation	Bernard J. Ransil, M.D., Ph.D. Boston City Hospital
Measurement and Enhancement of PROPHET System Performance	David D. Friesen First Data Corporation

Figure 3.

MAJOR NEW FEATURES IMPLEMENTED IN FY 1974

1. The data type SAMPLE
2. The data type MULTIMOLECULE
3. Molecular substructure search
4. Bulk data entry
5. TABLE/TEXT scanning
6. TABLE output on teletype/line printer
7. TABLE archiving
8. Terminal linking

Figure 4.

accretion of statistical procedures. The MULTIMOLECULE feature allows the visualization and manipulation of two or more molecular models in the same three-dimensional coordinate space, a capability of obvious utility for the study of molecule/molecule interactions. The substructure search option makes possible the selective retrieval from a file of molecular structure descriptions of only those molecules containing a specified subgraph. The remaining items contribute in their several ways to making the System more flexible and more convenient to use. Copies of the PROPHET System User's Manual are available on request to those readers interested in a more detailed description of these and other capabilities.

The PROPHET users also are developers of new System features via their own programming and their collaboration with the PROPHET contractors. Examples are (1) the contributions of scientists at Boston City Hospital to the design and refinement of the data analysis tools built into PROPHET, (2) the addition by scientists at Mount Sinai School of Medicine of multi-exponential fitting routines and tabulations of molecular parameter values having general interest to quantum pharmacologists, and (3) the addition by scientists at the Medical Foundation of Buffalo of new molecule-handling procedures (including the classic ORTEP molecular model diagrams) and a unique collection of three-dimensional structural descriptions of over 200 steroids. These and other user contributions are or will be highlighted in the PROPHET System Public Procedures Manual.

Still other new features come from outside the PROPHET community, for an important attribute of PROPHET is its ability to accept relatively gracefully large programs developed in other languages and on other computing facilities. This attribute was demonstrated in FY 1974 when the staff of Bolt Beranek and Newman Inc. arranged for Dr. W. T. Wipke of Princeton University to attach his molecular model builder to PROPHET. Dr. Wipke's work is generally acknowledged as the most nearly comprehensive algorithm for the generation of chemically plausible three-dimensional molecular models from only simple connectivity descriptions of substances, including those with arbitrarily complex ring systems. The capabilities of this program are scheduled to be offered to the PROPHET users via the COMPUTE MODEL command early in FY 1975.

An analogous major accretion in capability, this time in the area of mathematical tools for PROPHET users, is planned for FY 1975. CBIH Program contractors are designing and implementing a communication interface between PROPHET and MLAB, a powerful software system developed by Knott and Reece of NIH's Division of Computer Research and Technology for fitting various functional forms to experimental data. The immediate objective of the work on a PROPHET/MLAB interface will be to allow MLAB to operate on data contained in PROPHET TABLES. MLAB's capabilities should prove invaluable to PROPHET users for data summarization and should represent a significant step toward offering easy-to-use tools for modelling and simulating the behavior of pharmacological systems.

SYSTEM PERFORMANCE

No matter how diverse and sophisticated their information-handling capabilities, computer systems must also offer good service if they are to be welcomed into the milieu of computer-naïve biomedical scientists. And good service means many things: (1) hardware and telecommunications lines which function reliably all day long and every day of the week; (2) commands and other System features which perform "as advertised" in the various manuals; (3) assured integrity and privacy of users' files; (4) rapid System response, at least to simple requests; (5) low variance in command completion times within and between usage sessions; and (6) continuing introduction of System improvements with minimal impact on the appearance and availability of tried and true features. Making PROPHET "friendly"--and keeping it so--are high priority items for the CBIH Program.

The quest for friendliness exacts high costs in human, machine, and fiscal resources. Extracting reliable performance from graphic display terminals and telecommunications services is a never ending battle. Maintaining adequate System response times (while simultaneously making functions as easy to use as possible and conducting a vigorous development effort in parallel with the service effort) is proving to be a severe test of technological and managerial skills. Clearly, as the numbers of terminal sites and users continue to grow, the PROPHET contractors and staff not only must be careful to keep their demands on computer and telecommunications technology well within the state-of-the-art but also must be prepared to break new ground in the largely unexplored area of managing nationally shared computer resources for biomedical research.

A wide array of efforts focused on performance improvement is ongoing within the PROPHET project and still others are planned. In the area of enhancing efficiency, for example, the principal effort is continuous measurement and analysis of selected System utilization parameters under various conditions of user load. These studies help pinpoint where there are inefficiencies and processing bottlenecks and give rise to specific tasks designed to eliminate--or at least reduce the severity of--the key problems identified. Among these tasks in FY 1974 were (1) the addition of a special command for fast response, bulk data entry to TABLES, (2) recoding the substructure search routine to reduce its running time, and (3) initial development of a second pass compiler which performs efficiency optimization on programs written in the PROPHET base language (i.e., most of the System). Also, CBIH Program contractors and staff developed an overall strategy for upgrading and/or reconfiguring both central facility hardware and remote terminal hardware over the years immediately ahead. If fiscal constraints permit this strategy to be followed, the new hardware will do much to insure high quality service and will accommodate more users while decreasing operating costs.

SELF CRITIQUE

Evaluation of Federal programs is difficult at best and impossible at worst; and the obligation to do so seems most frequently honored in the breach. Those removed from day-to-day operations generally cannot wrap the correct context around their observations and impressions. Those "in the trenches" often find that adrenaline and introspection don't mix. Nevertheless, the question "Is this trip really necessary?" is as relevant to the PROPHET project as to other claimants on the public purse and deserves an answer. The reader of the following paragraphs hopefully will appreciate the gesture, indulge the euphemisms, and forgive the bias.

First, the good news! The PROPHET System has been in service for over two years and is working well. Pharmacologists who once were either intimidated or repelled by computer technology now find PROPHET an inextricable part of their research life. Pharmacologists who once made only low-level, arms-length use of computers via packaged statistical programs now practice a style of graphically oriented, interactive data analysis that is at times awe-inspiring. Pharmacologists who once limited their investigative horizons to data gathering and simple hypothesis testing now find they can formulate at least simple mathematical models and use them to organize their knowledge and guide their future experimental work. And finally, to include some management parameters, the PROPHET project after six years total effort is on course, on schedule, and within budget.

Now the litany of frustration and disappointment!

1. The PROPHET System is expensive. Making a comprehensive set of information-handling functions easy to use means very big computer programs and a very big machine on which to run them. The successes to date notwithstanding, PROPHET has a long way to go to be self-sustaining via user fees and/or readily replicable.
2. PROPHET service is often sluggish. The need to do development and service on the same equipment produces inevitable conflicts for machine resources. The conflicts usually manifest themselves as slow response, and users' productivity and satisfaction diminish accordingly.
3. The technology leaves a lot to be desired. Neither graphic display terminals nor digital telecommunication services seem able to withstand the challenge of PROPHET's demands without the near constant ministrations of well trained and high priced people.
4. PROPHET project management needs strengthening. The continuing operation and development of PROPHET involves an interdependent set of contracts whose constituent task orders must mesh cleanly for everything to function smoothly. After two years of service operation, there remain some areas where the corporate performance of contractors and NIH staff in responding to user problems and requests could be improved. Also, more attention to assuring the quality of the mathematical software is indicated.

5. The PROPHET System generally needs a protagonist before it penetrates a new research environment. The most successful terminal installations feature on-site at least one highly motivated user who feels personally responsible for helping System personnel to overcome problems and colleagues to appreciate PROPHET features that aren't intuitively obvious to the uninitiated. The only installation which failed during PROPHET's first two years of service might not have if the CBIH Program manager had paid more attention to cultivating such an advocate before a remote facility was established; for what should have been short-lived problems became chronic, what should have been minor hurdles became major obstacles, and the result was unsatisfactory to all concerned. The scientists at this site were justified in not adopting the System. The mistake was the CBIH Program manager expecting PROPHET to sell itself.
6. PROPHET protagonists are hard to find. While PROPHET clearly has succeeded in attracting to it many well trained scientists doing high quality work in the mainstream of pharmacology research, many others remain unaffected by knowledge of the System's existence or skeptical as to its value. By and large, the burden of proof still rests with those who advocate the technology and the expanded opportunities that powerful tools can offer a prepared mind.

OUTLOOK

Weighing both the promises and the problems in the balance, the outlook for the PROPHET System is encouraging. The stage is set for steady maturation as a nationally shared computer resource. There are no problems that shouldn't give way to good taste, good management, and enlightened tenacity. There are more high quality, enthusiastic applicants than capacity to accommodate them. The basic PROPHET tools have stabilized to a considerable degree. The capability for graceful accretion of important information-handling functions developed outside the PROPHET project has been demonstrated. The PROPHET users are finding more and more areas where the System enhances their research productivity. And PROPHET-mediated sharing of programs and data bases among geographically separate groups is beginning to be practiced.

The fruits of more than a half-decade of work are emerging. The harvest has begun.

APPENDIX

Description of the PROPHET System

The PROPHET System is a unique, large-scale computer resource designed and developed exclusively for the study of chemical/biological interrelationships. Its long-range goal is to accelerate the growth of a predictive science in this area. Its immediate objective is to facilitate a broad spectrum of laboratory and clinical investigations concerned with how chemical substances influence--and are influenced by--life processes. PROPHET seeks to fulfill both of these purposes by making powerful computer-based information-handling methods available to individual scientists in a convenient and easy-to-use form and by encouraging computer-mediated sharing of data, programs, and the like among PROPHET users.

The PROPHET System hardware/software complex is the result of over five years of effort by contractors, advisors, and staff of the Chemical/Biological Information-Handling (CBIH) Program. The software is an extensive array of highly integrated special-purpose programs designed and developed by Bolt Beranek and Newman Inc. (BBN) of Cambridge, Mass. The hardware is a time-shared, digital computer (a Digital Equipment Corporation PDP-10) acquired by the NIH specifically for the PROPHET project and housed and operated by First Data Corporation (FDC) of Waltham, Mass. A PROPHET user accesses the System remotely via a graphic display terminal (the Computek 400) communicating over telephone lines.

The PROPHET System has five features that jointly set it apart from other research computer systems:

1. It is established as a national resource especially for the community of scientists concerned with chemical/biological interrelationships.
2. It can be mastered readily by scientists who have little or no prior computer experience.
3. It can be applied effectively to a wide range of complex information-handling tasks relevant to chemical/biological interrelationships without the user having to write any computer programs.
4. It can accommodate very sophisticated users/programmers, integrating user-prepared procedures automatically into the basic System.
5. Through the medium of a set of standard logical frameworks (called data types) for organizing experimental data, molecular structure descriptions, and the like, it seeks to promote the sharing of information among users.

In short, PROPHET is neither a general-purpose facility nor an information service in the traditional sense. Rather, it is a computer resource whose information-handling power is deliberately concentrated in a few specific areas and whose capabilities can grow in a highly orderly way in response to users' requirements.

In its present form, the PROPHET System is primarily a tool for the management of experimental data and molecular structure descriptions. Conversing with the computer via a high level command language (which can be mastered in a matter of hours or days), scientists can, among other things, (a) define--and redefine at will--the structure of tables within the computer to accommodate their personal research data and/or data which they extract from the literature; (b) add to or alter the content of existing tables and produce displays of all or any parts of tables in either tabular or graphical form; (c) invoke a variety of information retrieval operations and/or statistical/mathematical operations on the content of these tables; and (d) share selected tables and/or programs with collaborators who reside at geographically distant locations. Moreover, for the specific case of molecular structure descriptions, commands are available to receive input of two-dimensional structural diagrams drawn with a computer-controlled stylus and tablet and to produce and manipulate displays of three-dimensional molecular models. And all the operations which can be invoked through the high level command language can be embellished by a user's own procedures written in a simple programming language (PL/PROPHET).

Current plans call for future versions of the PROPHET System to offer not only extensions to and refinements of the present capabilities for handling experimental data and molecular structure descriptions, but also commands and procedures for constructing and exercising models which simulate life processes. Prototype implementation of these modelling tools already is under way, with particular attention being paid to facilitating research in pharmacodynamics. With these emerging features, as with those currently available, emphasis is on the provision of a set of basic, easy-to-use modules which users may invoke, combine, and extend as their needs dictate.

Current plans for future versions of the PROPHET System also call for expanded capabilities and procedures for user-to-user communication and intracomputer "publication" of selected data files and programs. Special emphasis is being placed upon developing an integrated body of public programs and data from the contributions of individual users. While there is no desire to abrogate each individual user's right to maintain his or her personal files in a fully private status, users are being encouraged to share the results of their work with others who also have access to PROPHET.

Fiscal Year 1974
Annual Report
General Clinical Research Centers (GCRC) Branch
Division of Research Resources (DRR)

I. Introduction and Goals of the Program

The primary goal of the GCRC Program is the establishment of a resource for the clinical investigation of humans in order to increase the total body of knowledge of the etiology, progression, prevention, control and cure of human disease. To meet this goal certain objectives have been established, i.e. the establishment of a resource to:

- a. Increase the knowledge of human physiology and pathophysiology by the investigation of the epidemiology, etiology, and progression of human disease by direct studies in man;
- b. Provide an optimal setting for the performance of controlled studies by clinical investigators supported through NIH and other research support programs;
- c. Encourage and foster disciplinary interaction;
- d. Contribute to the maintenance of a national core of qualified clinical investigators; and
- e. Develop technological and therapeutic advances to ensure the expeditious translation of fundamental biological knowledge into effective patient care.

The GCRC Program evolved in response to the need for specialized facilities and trained personnel to meet the demands required by high quality clinical research. The study of human physiology and disease with its broad implications for the maintenance and restoration of health requires an optimal environment. Furthermore, a single specialized research unit effectively meets the needs of investigators studying a variety of categorical disease problems in the most effective and economic fashion.

In 1959, Congress expressed the view that the Nation deserved and should receive the benefits of basic research as rapidly as these became available. Passage of P. L. 86-798 established the legislative basis for the program, and in 1960 Congress appropriated \$3 million for the establishment of the GCRC's. These units were designed as a locus for clinical investigation; they were created to supplement rather than supplant the ongoing medical research in universities and hospitals.

The NIH defined a clinical research center as "a distinct organizational and physical entity providing a continuing framework for a clinical research effort, including the necessary laboratory, clinical, and supporting services."

A center would provide the skilled personnel and an optimal and secure environment for human research.

Specifically, a GCRC was to be a resource to a medical institution permitting enhancement of the quality of clinical investigation. This was accomplished by establishment of a discrete physical unit or research ward, apart from the general care wards, with the well trained staff needed for precise control and observation. The research conducted in the center derives its support from the various institutes of the NIH as well as from numerous foundations and philanthropic organizations. Funds from the GCRC Program were intended primarily for the establishment and maintenance of the separate discrete unit in which clinical research was done.

A center consists of four to 30 beds, the average number being eleven. A typical center contains bedrooms, treatment rooms, a core laboratory, diet kitchen, patient's lounge, nurses' station, and conference room. Centers can usually accommodate both adults and children but about one-fifth of the centers are entirely pediatric. Several centers specialize in areas involving premature infants, maternal-child, or acute surgical problems.

Over 13,000 individuals are involved with the centers. Center grants provide salary support for staff numbering approximately 1,800. Currently, the program consists of 83 centers supported through the Division of Research Resources, paying 83 percent of the extramural research patient care costs funded by NIH. Within the centers, senior scientists, research fellows, and house staff are exposed to increasingly sophisticated methods and concepts of clinical research. Such training is essential for the continued development of competent investigators and improved medical care in the Nation. An additional benefit of these centers is that future medical practitioners develop knowledge that facilitates critical evaluation of new medical discoveries with which they will be confronted in the course of their careers. In addition, the centers assist in the training of large numbers of paramedical personnel. They are usually the primary hospital facility in which nurses, dietitians, and laboratory technicians gain practical experience in newly developed patient care techniques.

The GCRC Program grew at an almost constant rate between 1960 and 1967. In the past few years, rising costs and fiscal restraints have prevented expansion and have forced support for fewer centers and a decreasing number of beds. During 1974, the GCRC Program supported 83 discrete inpatient centers plus two outpatient centers and one surgical scatter-bed center. The inpatient GCRC is a discrete center, is a geographical unit with a complement of research beds, a cadre of highly skilled research personnel, laboratory facilities, metabolic kitchen, and whatever supporting facilities are required to provide the rigid control and precise environment needed for clinical research. Scatter-beds are regular hospital beds normally used for patient care which may be utilized in certain situations for research purposes when they provide unique investigative opportunities.

Although centers exist in about two-thirds of the teaching medical institutions, a number of such institutions with great potential do not have centers. Table I depicts the program history since 1967. The Program has operated reasonably effectively in the face of sharp inflationary rises and modest budget increases through a number of adjustments, such as termination of support to a number of

centers, reducing the number of beds supported, savings realized through new discrete costing procedures, service patient policy, and some research carried out on an outpatient basis rather than an in-patient basis. Table II provides the results of a recent survey on the overall (professional, nursing, dietary, etc.) personnel cost increases per position since FY 1969.

Table I GCRC Program, FY 1967 - 1975

<u>Fiscal Year</u>	<u>Medical Schools</u>	<u>Number of Centers</u>	<u>Funded Beds</u>	<u>Patient Days Funded</u>	<u>Full-Time Equivalent Positions Funded</u>	<u>Apportionment (in thousands)</u>
1967	62	91	1131	260,176		\$ 28,463
1968	62	91	1051	277,663		30,443
1969	64	91	1023	284,064	2,297	35,004
1970	64	93	940	252,094	1,920	35,004
1971	56	82	881	238,227	1,885	38,004
1972	58	84	907	246,638	1,867	42,181
1973	59	83	903	239,167	1,790	41,300
1974	63	83	890	228,417	1,767	42,405
1975	63 est.	83 est.	840 est.	200,000 est.	1,700 est.	42,485 est.

Table II
% Increase In Personnel Costs,
FY 1969-1974 (in thousands)

<u>Fiscal Year</u>	<u>Ave. Cost/Postion</u>	<u>% of Increase</u>
1969	8,335	-----
1970	9,244	10.9
1971	10,228	10.7
1972	10,985	7.4
1973	11,746	6.9
1974	12,785	8.8

Despite budgetary constraints in recent years, the program continues to support the best available resources for clinical research. Roughly two-thirds of all hospital beds in the Nation specialized for research on humans are supported by this program.

During 1967-74, a dynamic exchange of beds and centers has occurred within the program. In 1967, 1,131 beds were approved in 91 centers. In subsequent scientific reviews, 23 centers with 192 beds were disapproved and NIH support terminated. An additional 251 beds on the basis of limited scientific productivity in 46 centers were eliminated with corresponding staff reductions. During this same period, 12 new Centers and six reapproved centers (with revised applications of higher scientific merit) for a total of 161 beds were funded. In addition six of the centers given two year renewals have worked closely with staff in revising their programs to compete successfully with programs of higher scientific merit. The net result has been a substantial improvement in the overall scientific quality of the program and the funded beds now correspond

closely with the bed needs of investigators holding NIH-sponsored grants and contracts. Despite these reductions and modest increases in appropriated and apportioned funds, rising costs have outstripped available funds. This differential has been met in part through appropriate collections from third party carriers initiated in 1970 and in part by encouraging investigators to carry out some of their activities through less expensive outpatient protocols, whenever feasible.

II. Modifications and Innovations

Through the years, the GCRC Program has been responsive to the changing needs of the GCRCs by modification of program components. The Branch has also been active in anticipating the needs of the centers and in generating and developing resources which facilitate clinical investigation. The following is a list of some of the program modifications and innovations of the past seven years:

Outpatient Program

With program funds becoming progressively exiguous and with escalating hospitalization and personnel costs diminishing the value of available funds, an optional outpatient program was initiated in 1970. A capability in ambulatory patient research enables more latitude in clinical research protocols and promotes maximum efficiency of research dollars. To date, 50 centers have exercised this option and two centers have applied for and received support for separate outpatient facilities. It is estimated that approximately 40,000 outpatient visits will be conducted at the centers in FY 1974.

Service Patient Policy

In 1969, program policy was modified from supporting solely inpatient research to allowing grantees the option of admitting category B, "service patients" to the center. A category B service patient is "a patient admitted to a GCRC primarily for care, but who is also participating in a research protocol".

Service patients are fiscally responsible for their care in the GCRC, as they would be if admitted to a regular hospital bed for treatment or diagnosis. However, when patients participate in a research protocol the center is charged for that portion of their hospitalization.

Clinical Research in Surgery

Because GCRCs are not designed to provide surgical services, research in surgical procedures is somewhat limited. An experimental award was made to provide an institution with surgical resources for clinical research. The GCRC Branch anticipates that an evaluation of the research productivity will be made in the near future.

CLINFO

CLINFO is a scientific inquiry sponsored jointly by the Biotechnology Resources and the GCRC Branches of DRR. It is aimed at identifying and characterizing the intellectual tasks and information flows in clinical investigation and at

developing methods for facilitating these tasks and flows, possibly with the aid of computers. It was initiated in 1972 subsequent to recognition by DRR that a need for a better information system existed in the clinical investigatory process. Currently, a consortium of clinical investigators and a computer contractor is studying the problem.

Discrete Unit Costing

In 1970, the GCRC Branch developed a new accounting method for discrete bed centers in hospitals whereby "space charges" are negotiated and paid on an annual basis, while ancillary services (x-ray, laboratory, etc.) are charged on an item-by-item basis. This has resulted in substantial savings in many centers and in better management of center dollar resources. Negotiation of these current rates has lagged due to regionalization of the Office of Grants Administration Policy, DHEW. Additional staff is needed in the GCRC Branch to expedite these negotiations to realize the full potential savings possible.

Contribution Papers

To demonstrate some significant GCRC resources contributions towards the accumulation of new medical knowledge, a series of contribution papers were written by center investigators and by GCRC Branch staff. The contribution papers which are available from the Branch are:

- a. Atherosclerosis Contribution Paper: The Roll of Clinical Research in the Development of Knowledge in this Medical Area.
- b. Growth and Development: Research into the Early Years of Life
- c. Drug Abuse
- d. Studies on Narcotic Addiction
- e. Diabetes
- f. Sickle Cell Anemia
- g. Cancer
- h. Transplantation

Annual Ranking of Centers

Anticipating continuing inflation and relatively fixed budgets, the GCRC Branch staff, also in 1970, devised a mechanism by which centers of lower scientific merit may be identified and withdrawn from program support equitably and with minimal disruption to the program as a whole. Under this new mechanism each new or renewal application is reviewed in its preterminal year and is ranked along with all other new and renewal applicants reviewed within that fiscal year. Among other advantages, centers face uncertainty as to their continuation in only the preterminal year of each project period. Once support is committed, a center can, within reasonable limits, be assured of continued support until its next competitive review.

Resource-Related Research Grants

The Resource-Related Research Project Grant was established in 1973 to improve the research capabilities of the GCRCs through application of existing scientific technologies to clinical research or through development of new, or modification of existing, technologies and their application to clinical research.

Clinical Associate Program

Meritorious investigation necessitates the maintenance of a highly qualified core of clinical investigators. Until recently, training of these investigators was supported by various training programs. In fiscal year 1971, a total of \$206,979 in fellowship support, \$3,205,048 in research development awards, and \$17,386,305 in training grants were identified as support for projects using the GCRCs. Because the status of this support is uncertain, it may become increasingly difficult to meet the objectives of the GCRC Program.

To compensate for this projected loss of scientific manpower, the GCRC Program instituted the Clinical Associate Physicians Program in October 1973. This program is work-oriented to accomplish the following research goals:

1. Provide competent senior clinical investigators undertaking studies on GCRCs with an important component of the research team to satisfactorily accomplish their research goals.
2. Provide an opportunity for promising young medical scientists with demonstrated aptitude in research to develop into independent clinical investigators.
3. Supplement professional patient care for patients on the center.
4. Provide core laboratory direction and assistance by clinical associates.

To date, nine centers have approved clinical research associate positions.

Mixed Centers

A few centers have been tried where a limited number of Category C service patients (not on a research protocol) are mixed with research patients. This has proven a satisfactory method of center operations in select centers provided proper administrative controls are exercised.

NIH Clinical Research Coordinating Group

In FY 1973, the General Clinical Research Centers Program provided 83% of the NIH-awarded research patient care cost and the categorical Institutes provided \$108 million to investigators using the General Clinical Research Centers. A coordinating group, established in 1974, will facilitate the effective interaction of NIH extramural clinical research, ensuring that the maximum potential

of clinical research resources be realized. With increasing contract agreements being established, a Coordinating Group will recommend uniform policies for using contract funds to offset "ancillary" studies on patients hospitalization on the Centers.

Third Party Payments

In 1970, the Program initiated a policy of charging third parties for patients on the research centers for time which they would normally have been admitted for therapy. Table III presents the dollars that have been credited to the General Clinical Research Centers Program in 1972 and 1973.

TABLE III

Service Patient
Credits to the
GCRC Program

<u>FY</u>	<u>Credits</u>
1972	\$2,935,282
1973	\$3,354,985

This practice is now yielding nearly a ten percent saving of funds.

Program Evaluation

The General Clinical Research Centers Branch undertook a program-wide review in response to a DHEW evaluation policy stated by the Secretary in an October 1, 1969, memorandum which states in part:

We are faced with stringent budgets in the years ahead. This challenges all of us to insure that the programs this Department administers are having maximum impact. I have told the President and the Congress who are also very much concerned about the effectiveness of our programs that we will meet this challenge by making a comprehensive effort to improve their management and determine how successful our programs are in reaching their objectives. This requires a substantial increase in the evaluation efforts of the operating agencies and the Office of the Secretary, all of whom have an important role to play.

The evaluation began in December, 1971. A General Clinical Research Centers subcommittee was established to advise and assist staff. A staff committee comprised of the General Clinical Research Centers Branch scientific and grants management staff, Program Analysis Branch staff, and the Special Assistant for Program Evaluation, DRR together with the subcommittee, devised an evaluation format consisting of three phases in which objectives were defined, program components were evaluated, and recommendations were formulated. This formal in-depth review ended in February, 1974. The evaluation data was assembled and

critically reviewed by the General Clinical Research Centers Branch, the Office of the Director, DRR, the General Clinical Research Centers Committee, and the National Advisory Research Resources Council, with respect to the achievement of each specified objective.

The following summarizes the evaluation evidence that the program achieved its stated goals:

Goal #1. For the clinical investigation of humans in order to increase the total body of knowledge of the etiology, progression, prevention, control, and cure of human disease.

In FY 1974, there are 83 General Clinical Research Centers utilizing approximately 890 research beds in 76 institutions, including 63 medical schools. More than 83% of NIH support of research patient care cost in 1972 and 1973 was provided by the General Clinical Research Centers Program.

Goal #2. To increase the knowledge of human physiology and pathophysiology by the investigation of the epidemiology, etiology, and progression of human diseases by direct study in man; and with this knowledge develop technological and therapeutic advances to ensure its expeditious translation into effective patient care.

The Contribution Papers (see page 71) highlight selected areas of the investigations undertaken on the Centers and illustrate the vital role the centers had in elucidating disease processes and developing effective preventive and therapeutic measures.

Publications and presentations were tabulated for FY 1971 to demonstrate the scope of research and quantitative investigative productivity. A total of 3,911 publications appeared in 481 books and journals and were presented at 522 scientific meetings, and were attributed to research performed on the centers.

Goal #3. To provide an optimal setting for the performance of controlled studies by clinical investigators supported through NIH and other research support programs.

General Clinical Research Center investigators reported DHEW support of their research, other than General Research Support and General Clinical Research Centers Branch support, for the years FY 1970, FY 1971, and FY 1972, was \$91,178,222, \$94,126,380, and \$108,574,618, respectively. More than 95% of this federal support came from NIH. By FY 1972, General Clinical Research Centers investigators reported nonfederal support from 305 grants from 173 foundations and private sources to support 628 protocols. Program Directors and their assistants competed successfully for \$9,094,995 of non-GCRC support from 125 NIH grants and contracts in FY 1971.

Goal #4. To encourage and foster disciplinary interaction.

Anatomical and pathophysiological codes of the types of research performed on the GCRCs was developed by the Program Analysis Branch to indicate the magnitude of studies in various bodily systems. These data were compiled for FY 1970, 1971, and 1972 and indicate the broad range of research being conducted at the GCRCs. A listing of the numbers and titles of research protocols, patient discharges, patient days, and approximate GCRC dollar support for the various anatomic and pathophysiologic codes is available from the GCRC Branch.

Goal #5. To contribute to the maintenance of a national core of qualified clinical investigators.

In order to determine the commitment to medical research training on the GCRCs, the number of medical students, interns, residents, fellows, dietary interns, and nurses trained on these centers in FY 1970 and FY 1971 as part of their educational experience in research was tabulated. About 3,000 students trained on the centers in FY 1970 and FY 1971. In addition, approximately 4,000 house staff and fellows trained on the centers in FY 1970 and FY 1971. Approximately 1,000 nurses and dietary interns received training during FY 1971 and it is believed that the educational experiences in research will influence their careers in clinical investigation. An additional means of contributing to the maintenance of a national core of full-time personnel dedicated to clinical investigation is through the direct support of professionals. In FY 1971, Program Directors and their assistants received direct salary support for 124.4 full-time equivalent positions.

As a result of the evaluation study, a number of recommendations have been formulated and are in various stages of implementation. These recommendations are briefly discussed below.

1. Annual Ranking of Centers (see page 71)

Since 1970, a ranking system based on peer review by the best available scientific talent has been developed and refined with the GCRC Committee and National Advisory Research Resources Council. The system allows competition between new centers of excellence and existing centers and permits continued upgrading of the quality of the program. This system should be continued.

2. Outpatient Research (see page 70)

It is recommended that this program be expanded where possible; it appears to be an effective means of increasing clinical research opportunities in selected areas at moderate cost.

3. Third Party Payments (see page 73)

It is recommended that this policy be continued and refined to maximize research dollar efficacy.

4. Clinical Associate Program

It is recommended that this Program be continued.

5. Mixed Centers (see page 72)

This method of operation deserves further evaluation because it allows flexibility in matching center bed size to scientific need and productivity.

6. Discrete Unit Costing (see page 71)

Additional staff is needed in the GCRC Branch to expedite negotiations to realize the full savings potential.

7. CLINFO (see page 70)

Implementation of a data collection and analysis system (CLINFO) may facilitate investigations in the GCRCs. Further investigation is being done to determine the feasibility and applicability of this project.

8. Contribution Papers (see page 71)

These papers seem to be effective in illustrating program accomplishments. They illustrate the vital role the centers had in elucidating disease processes and developing effective preventive and therapeutic measures.

9. Resource-Related Research Grants (see page 72)

It is recommended that this type of research grant be further evaluated as an instrument to stimulate the development of techniques derived from mathematical, engineering, and biological sciences for use in the GCRCs.

In summary, the evaluation has provided an opportunity for in depth study of the program by Branch and Division staff and its extramural advisors. Several areas for further study have been identified and are in various stages of exploration, including new methods of center operations.

Data from the evaluation study have been presented to extramural advisory groups, and to the NIH Executive Committee on Extramural Affairs and will be used in program review activities during the coming year. A major difficulty has been the lack of staff resources to adequately execute a number of identified potentially fruitful activities.

The following documents are available as the full evaluation report:

- | | |
|----------|--|
| Volume I | 1. History of the General Clinical
Research Centers Program |
| | 2. Program Data Paper |
| | 3. Contribution Papers |
| Volume 2 | 4. Program Modifications and Innovations Document |

III. Training

A paramount problem today in the area of clinical research is the dwindling number of talented senior investigators with the growing demands on their research time because of increased teaching, service, and administrative responsibilities. The program serves an important function by providing institutions with an essential resource where young physicians participate in the work of experienced clinical research teams and assist busy senior investigators.

Within the centers, senior scientists, research fellows, and house staff are exposed to increasingly sophisticated methods and concepts of clinical research. Such training is essential for continued development of competent investigators and for improved medical care of the Nation. In these centers, future medical practitioners develop foundations of knowledge that facilitate critical evaluation of new medical discoveries with which they will be confronted in the course of their careers. In addition, the centers assist in the training of large numbers of paramedical personnel. They are the primary hospital facility in which nurses, dietitians, and laboratory technicians gain practical experience in newly developed patient care techniques, generally resulting in better quality of hospital care. Table III shows the numbers of individuals receiving training in the GCRC during the past five years.

Table III. Training in GCRCs, 1968-1972

	1968	1969	1970	1971	1972
Medical Students	2538	2939	3065	2872	3152
Interns	863	1019	911	921	873
Residents	1576	1870	1751	1646	1745
Fellows	1227	1340	1321	1169	1281
Dietary Interns	404	422	487	578	460
Student Nurses	697	1066	1089	914	944

IV. Fiscal Summary

Figure I gives program appropriations ceilings since 1966. Appropriations have not been adequate to meet recommended expenditures. It can be seen from Figure II that personnel and hospitalization costs have been the key factors in the rising costs of the program. Despite the decline in beds, hospitalization and personnel costs have continued to increase.

V. Program Highlights

As will be seen, investigators have used centers for the study of virtually all aspects of human disease. The scope and vigor of the supported clinical research is demonstrated below by presenting scientific highlights, the summaries of which were submitted by individual centers as examples of promising work in progress. The following highlights a few of the major areas of interest and accomplishments among the centers.

Respiratory Distress Syndrome (RDS)

Over the past decade, the rate of survival of infants with Respiratory Distress Syndrome (RDS) who require mechanical ventilation has not increased rapidly. Recently, a modification to a Bennett PR-2 Ventilator was accomplished so that a positive end-expiratory pressure could be provided as well as continuous flow. Now in use for one year, these modifications have been responsible for an increase in the overall survival rate of infants with RDS to 79% from previous rates of 60% in the years 1969-1972. The incidence of bronchopulmonary dysplasia and "respirator lung disease" during the past year has also been reduced considerably. Thus, the simple modifications of equipment have reduced both morbidity and mortality in premature infants with severe RDS requiring mechanical ventilation.

Infectious Disease

Adenovirus infections are one of the most common infections in infancy and childhood. Illnesses are usually mild but, on occasion, severe illness including pneumonia and death may result. At one center, investigators developed a vaccine which has afforded significant protection to those patients vaccinated. This offers a new approach for the prevention of adenoviral illnesses in infants and children.

Sickle Cell Disease

At one university, the Departments of Human Genetics and Internal Medicine, in collaboration with the Department of Internal Medicine, Divisions of Hematology and Nutrition, have explored the treatment of sickle cell disease with zinc. The investigators have shown that samples of red blood cells, hair and nails show evidence of zinc deficiency in about 20% of patients with sickle cell disease. Urine collections show that there is an increase of urinary loss of zinc in this disease and it is postulated that when red blood cells hemolyze within the blood stream, zinc is released and then excreted in the urine. The delayed puberty, decreased growth and poor wound healing, particularly of chronic leg ulcers commonly seen in this disease, are similar to the findings in zinc deficiency in patients in the Middle East and in experimental animals. Preliminary studies seem to show that when zinc is given intravenously it is removed from the blood and taken up by the tissues more rapidly in zinc deficient sickle cell patients than in normals. When zinc was given as therapy for patients with sickle cell disease, leg ulcers did seem to improve, growth occurred in a boy with retarded growth, and pubic hair appeared in a boy with late puberty.

Hematologic improvement occurred in one patient but was not obvious in five other patients. Thus, a new treatment has become available which, if preliminary observations are confirmed, could lead to a distinct improvement in the management of some patients with sickle cell disease.

Blood Lipid Abnormalities in Children and Adults

Atherosclerotic cardiovascular disease is the major cause of death and disability in the United States and several other industrialized nations. The causes of atherosclerosis are complex but probably the most important single factor is the relationship between elevations in the concentrations of cholesterol in blood and the rate of development of atherosclerosis. One of the major ongoing research projects in one pediatric center has been the development of normal values of the various blood lipid fractions (cholesterol, cholesterol esters, low density lipoprotein cholesterol, triglyceride, phospholipid, and free fatty acids) at various ages, and the study of those factors which may result in abnormal concentrations of the blood lipids. In addition, work has been directed toward the detection of children at risk for the development of atherosclerosis. Studies are currently in progress involving various modes of intervention, including dietary change and drug therapy. These studies have indicated that approximately 1 to 2% of apparently healthy adolescent school children have abnormal elevations in cholesterol concentration and approximately twice that number have triglyceride values that exceed the accepted normal distribution. In family studies carried out on such children we find that something less than half of the detected abnormalities are explained on the basis of familial or genetic abnormalities of cholesterol or triglyceride handling. It is in this group of children that the probability of early development of heart disease is high. In preliminary dietary intervention studies, approximately half of the abnormal patients have been normalized by dietary change. Drug therapy has been applied to a much smaller group of patients. Results from these observations are still pending. Of special interest is the finding noted for the first time that the very high lipid levels routinely seen in children with severe liver disease can be normalized by the administration of the drug phenobarbital. The mechanism by which phenobarbital results in lowering of blood lipid levels is under further study. Furthermore, phenobarbital is now being used in a group of children and young adults with inherited high cholesterol but without evidence of liver disease.

Of additional special interest is the recent observation regarding the blood lipid concentrations in families (parents and siblings) of children with diabetes mellitus treated in the clinic. Patients with diabetes mellitus were placed on a diet quite similar to the so-called "prudent diet" presently recommended by the American Heart Association and other groups as the type of diet which should be utilized for most Americans, and the entire family utilized the same diet as the diabetic child. Detailed lipid analysis in over 50 families in which the child has had longstanding diabetes mellitus revealed that the mean cholesterol and triglyceride levels in the fathers, mothers, and normal brothers and sisters of these children are well below the mean concentrations of cholesterol and triglyceride obtained in age and sex matched controls in the general population eating a normal American diet. A preliminary conclusion from this study is that the "prudent diet" is

acceptable to most families and is effective at lowering lipid levels. Whether this will have a longterm beneficial effect in lowering the incidence of cardiovascular disease in these individuals remains to be seen.

Cardiovascular Disease

Studies conducted at several centers involve the effect of direct revascularization surgery as therapy for coronary artery disease. Patients have been studied after direct revascularization and the state of their myocardium compared before and after surgery. From these studies, it appears that these procedures produce significant benefit in some patients.

Hypertension

Preliminary studies in a group of hypertensive patients suggest that patients with normal renin hypertension can be divided into two groups on the basis of renin-aldosterone responses to acute volume depletion. This has profound therapeutic implications in that, on the basis of this screening test, the physician would be able to determine which of his hypertensive patients will have a therapeutic response to diuretic therapy. Further work is under way to clarify these findings.

Alcoholism

Of this country's ten million alcoholics, many will die prematurely from disease secondary to alcohol consumption. Investigators at one center discovered that the administration of moderate amounts of alcohol to normal subjects does not influence plasma triglyceride levels, but alcohol administration to subjects with a preexisting elevation in plasma triglycerides causes a further elevation. Therefore, since elevated triglyceride levels predispose to myocardial infarction, alcohol may well be more deleterious to that segment of the population with preexisting hypertriglyceridemia.

Liver Disease

Hepatic cirrhosis is the fourth leading cause of death in American males aged 45 to 54 years, is increasing in incidence, and is particularly prevalent in large American cities. Blockage of the blood flow through the cirrhotic liver results in increased venous pressure and sometimes sudden severe gastrointestinal bleeding. Determination of blood flow patterns in cirrhotic and bleeding patients is important in deciding which operation may best serve a patient. Study of such blood flow patterns in cirrhotics is now possible using a technique which provides access to the portal venous system and direct portal blood flow determination. Sudden deprivation of blood flow to the liver may be avoided by proper selection of operation in a particular patient. If perfusion of the liver can be maintained postoperatively, liver failure (the most common cause of death in cirrhotics following such necessary operations) could be avoided in a number of patients suffering from this common disorder. The availability of a new shunting procedure (Warren Shunt) developed in a GCRC now allows preservation of most of the blood flow to the liver in those patients in whom a high liver blood flow is found preoperatively by this technique.

Amino Acid and Protein Requirements of Man

Investigators at one GCRC have used new techniques to explore protein metabolism in humans and to define the metabolic response to alterations in the level of protein intake. A potential practical outcome is the development of sensitive diagnostic tools for evaluating protein nutritional adequacy. It will also lead to an understanding of the changes which occur in disease states and lead the way to a definition of the appropriate nutritional therapy. Another portion of this program has been concerned with the development of new techniques for assessing the needs for amino acids which cannot be made by the body and must be diet supplied. These are called the essential amino acids and their concentration in various protein sources determines how well the food source meets the human requirements. They developed a new approach for estimating the physiological needs for these amino acids, and studies conducted in people of 70 years or older indicate that the essential amino acid requirement does not increase with aging. Appropriate dietary programs provide an essential component of comprehensive medical care. These studies are providing an orderly accumulation of nutrition knowledge and offer a basis for the design and implementation of dietary regimes which should best meet the needs of people for achieving a maximum resistance to disease.

Cancer

Treatment of malignant disease by altering the patient's immune response represents one of the most exciting and innovative approaches to cancer therapy of the past decade. A recently employed tool for altering cellular immunity is transfer factor, a small molecular weight substance obtained from white blood cells. Preliminary trials of transfer factor therapy in acute leukemia, solid tumors, and fungal infections have resulted in a better understanding of which diseases and which stages of a disease are most likely to respond to this type of therapy.

Surgical Research

In an ongoing project, the blood flow capability of femorotibial bypasses for salvage of severely ischemic lower extremities is being studied. Recently, it has been shown that the limb salvage in patients with arterial blockage can be achieved by bypassing to the very small vessels of the distal lower extremity (as low as the ankle or below). This surgical technique has enabled limb salvage in 51 of 79 patients recently operated on in whom primary amputation above or below the knee would have been necessitated if standard operative techniques were employed. Evaluation of the long-term effectiveness of this new procedure and the blood flow capabilities of such distal bypasses continues. Additionally, newer techniques for producing improved grafts capable of function when used for distal bypass is being evaluated in an effort to salvage, from amputation, severely ischemic lower extremities in patients suffering from arterial disease.

Nutritional Management of Outpatients with Chronic Renal Failure

In studies published this year, it was shown that nutritional therapy can substitute for dialysis in selected patients with chronic renal failure. By supplying building blocks of proteins, together with a low protein diet, accumulation of waste products which require excretion is diminished. In patients with at least 2% of kidney function remaining, it has been shown that dialysis can usually be avoided altogether; in subjects with less renal function (or absent function), the interval between successive hemodialyses can be substantially prolonged.

The impact of such management upon the health care problem of chronic kidney disease could be expected to be highly significant in view of the massive expenditures now required for chronic hemodialysis in a substantial fraction of the population. To evaluate the full expectations and limits of such a program requires that large numbers of outpatients be evaluated with careful observation of patient progress and well-being. Such studies are now ongoing in an outpatient GCRC setting with the expectation that (a) the interval between dialyses can be extended in patients with kidney failure who require artificial kidney maintenance; (b) the need for hemodialysis can be temporarily eliminated in many subjects who have insufficient kidney function; and (c) the beginning of dialysis treatment can be forestalled in subjects with impending kidney failure and perhaps progression of the underlying disease can even be delayed.

Clinical Evaluation of Home Peritoneal Dialysis Equipment

In the past five years, a radically new concept for peritoneal dialysis has been developed which consists of permanent implantation of silastic peritoneal catheters into patients requiring dialysis for irreversible kidney failure. One such implanted in 1967 is still functional resulting in a home peritoneal program and rehabilitation of the patient. This method expanded to the treatment of many patients and has found wide acceptance in the United States.

During the past year, a number of automated peritoneal dialysis machines were developed and tested on patients on a GCRC. The machine permits the preparation of sterile, pyrogen-free dialysis solution from tap water and a sterile sugar-electrolyte concentrate at the bedside. The new system is simpler and safer to operate than conventional machines, thus permitting home dialysis for patients who cannot master the more complex hemodialysis machines. Particularly it has been helpful in facilitating home dialysis in small children. In addition, the new system costs less to manufacture and, in comparison with conventional dialysis machines, the cost of maintenance has been reduced by 75%. Five prototypes of this new system were tested in the past year with simultaneous home training for the patients or their parents. The evaluations included bacteriological studies, electrical-mechanical reliability, safety functions, machine-patient interaction, and ease of handling in a clinical or home setting.

Based on experience with this new system evaluated on a GCRC, it is believed that peritoneal dialysis will become a widely used, major treatment modality for chronic renal failure, supplementing chronic hemodialysis and renal transplantation. Small children and older patients, notably those with cardiovascular disease, will benefit most from these developments.

POST-TRANSPLANT HYPERTENSION

Renal homotransplantation in man is associated with a post-transplantation hypertensive incidence of about 20 percent. The cause of this hypertension was unknown, but attributed to corticosteroid therapy. Using the facilities of a GCRC, thirteen hypertensive post-transplant patients and six normotensive post-transplant patients underwent angiography, transplant vein catheterization, and Xenon ¹³³ blood flow studies six to 38 months following renal homotransplantation. All patients had comparable steroid dosage. Transplant vein renin activity was five times higher in the hypertensive patients. Angiography showed abnormalities of cortical vessels in eight hypertensive patients correlating with biopsy findings of chronic rejection. Hypertensive patients could not be distinguished from normotensives by pre-transplant blood pressure, type of donor, presence of old kidneys, original disease or glomerular filtration rate.

The tentative conclusions of the study were: (1) hypertensive patients, following renal homotransplantation, are characterized by low cortical blood flow and high renin activity resulting from transplant artery stenosis and/or chronic rejection, and (2) knowledge of sodium balance is necessary to interpret renin activity in post-transplant patients. The results completely refute the widely held belief that post-transplant hypertension is the result of corticosteroid therapy.

Epilepsy

Epilepsy is a major public health problem in this country, affecting between two and four million persons. Despite many drugs, a large number of patients remain insufficiently controlled to be able to lead normal lives. At one GCRC, a large clinical effort in the alleviation of epilepsy has taken place. Better methods for classification, seizure identification, and treatment have been developed on the basis of advances in technology, including the use of videotaped seizures with simultaneous electroencephalography and the development of telemetering capability.

Withdrawal From Opiate Dependence

Results from a study at a GCRC indicate that one can entirely withdraw narcotics addicts on known doses of methadone in less than 24 hours using gradually increasing dosages (administered intravenously) of the narcotic antagonist naloxone. The withdrawn patients were nonresponsive to additional doses of the antagonist within 24 hours and thereafter had mild abstinence signs which generally could be treated using tranquilizers on an outpatient basis. Twenty-seven addicts were so studied. The same program works equally well with patients addicted to heroin, Diluadid, oxymorphone, and methadone. The program has been so well tolerated that several patients

were treated as outpatients and allowed to give themselves injections of naloxone. In the longterm followup of patients so treated more than half of the patients have not relapsed to the use of narcotics.

The fact that addicts will volunteer for treatment in which they give themselves medication bringing on moderately unpleasant abstinence signs indicates the necessity for a radical revision in the psychological conception of the narcotic addict.

Schizophrenia

Schizophrenia is a psychiatric disease chronically disabling thousands of Americans and partially disabling thousands more. Psychiatric research has indicated an inherited predisposition and suggested that the basis of schizophrenia may not be strictly emotional or environmental, but that there may be a biochemical defect susceptible to therapy. While drugs introduced in the last few years have dramatically helped many schizophrenics and enabled them to leave institutions, the cause of schizophrenia has remained elusive and specific therapy is not available.

Studies performed on a GCRC have established a new postulate for a biochemical cause of schizophrenis in some patients or patients predisposed to schizophrenia. It is a theory which is susceptible to study and which has excited researchers in the psychiatric field.

Studies have suggested a mechanism by which a deficiency of folic acid could interfere with normal brain chemistry and suggest that this deficiency, or other defects in the same chemical pathway, could be of importance as a predisposing factor in a number of patients with schizophrenia. Further studies are in progress to establish the role of this, or similar defects, and of folic acid in general as a cause of schizophrenia.

Psychosomatic Illness

In dealing with diabetic children manifesting emotional arousal by going into diabetic ketoacidosis (i.e., diabetic ketoacidosis for these children represented a true psychosomatic illness), a conceptual model was formulated at one GCRC for psychosomatic illness in children. This model outlines the interactional characteristics of the "psychosomatogenic" family and the role of the child in family conflicts. In order to test this model in a prospective and scientific manner, a family task was devised in order to evaluate the interactional characteristics, and a family diagnostic study was devised in order to test the role of the child in family conflict. Free fatty acids were used as a marker of emotional arousal during the diagnostic interview since they also played a key role in the metabolic process leading to the psychosomatic symptom in these children, that is, diabetic ketoacidosis. The results in these diabetic children were highly encouraging, both from the point of view of validating the conceptual model for psychosomatic illness and also in terms of deciding upon appropriate therapeutic intervention.

With this model, investigators focused their attention on illnesses traditionally viewed as major psychosomatic problems, such as anorexia nervosa, a clinical syndrome characterized by voluntary refusal to eat and associated with a loss of greater than 20% of body weight. This disease has been associated with prolonged hospitalizations, and frequent relapses have characterized the clinical course. Deaths have occurred in some 10 to 15% of the patients and longterm followup studies indicate a success rate of less than 50%.

The research aspects of this study are now being analyzed. Videotapes of the family task and the family diagnostic sessions will be rated in order to test the hypotheses outlined previously. Preliminary results are highly encouraging and indicate that free fatty acids, which had been used as a marker of emotional arousal during the family diagnostic interview, do not correlate with the psychological ratings. On the other hand, the success rate of this program has been extraordinary: in contrast to the previous reports in the literature the current success rate is 90%. Indeed, the only failures of the program have been those in which the family was withdrawn from therapy. Success is defined as a child for whom eating is no longer a problem, who has appropriate peer relationships, and where no new symptom has appeared either in that child or other members of the family.

VI. Future Objectives and Trends

A. Resource-Related Project Grants.

This program serves as an administrative locus for projects which aim to upgrade clinical research capabilities through development or adaptation of technical or conceptual tools for use in GCRCs. The Branch had not implemented this project because of fiscal constraints in the entire program. However, with the recent release of impounded funds, the Branch initiated the program and is currently reviewing 5 proposals.

B. Clinical Research Center Associates Program

To ensure that the greatest potential for clinical investigation can be appropriately achieved, applications for GCRC Associates will continue to be reviewed. It is expected, however, that the number of center associates will be limited inasmuch as high quality research is one of the prerequisites.

C. General

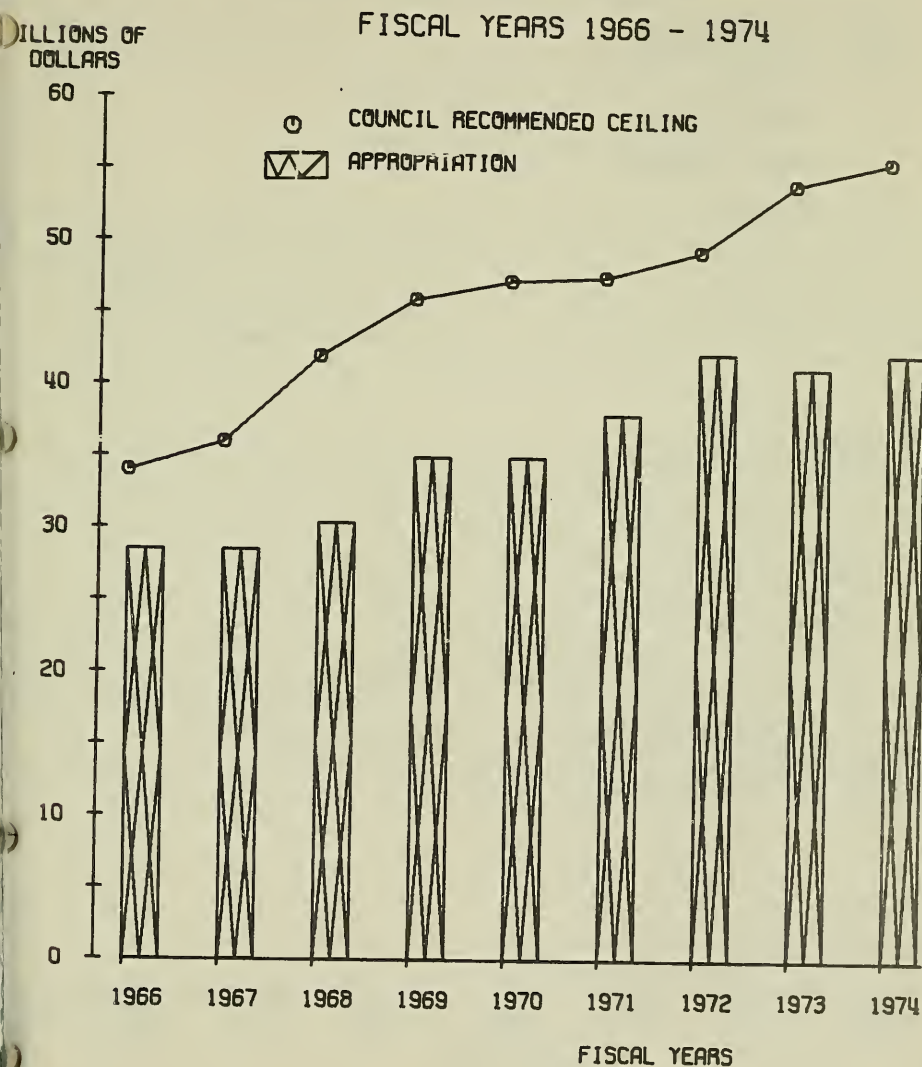
The proposed budget for FY 1975 shows a modest increase over the levels previously available and would require further program retrenchment commensurate with the diminished purchasing power of the dollar. During the past three years, the program has been maintained at a relatively stable level through savings achieved by trimming less essential positions, reducing the number of beds, savings from the service patient policy now amounting to almost ten percent of the budget, and shifting appropriate research protocols to an outpatient basis. Our current assessment of center activities leads us to believe that further significant savings through these technics are

unlikely without eroding the research productivity within the program. It is possible that some additional savings may be achieved with the operation of a few mixed units in limited numbers.

During the past several years, the program has attempted to maintain optimal clinical research productivity through an annual ranking of centers and projects competing for available funds. We plan to continue this process. Last year those centers in their preterminal year which were near the funding cutoff line were held over for an additional year to compete with applications in their preterminal year this year. Thus, in addition to the 17 competing grants and four new applications which will be evaluated by the Committee and Council in May and June, there are four or five hold over grants from last year which will be included in this year's annual ranking. The centers of greatest scientific productivity will be assured funding with less meritorious centers being held over to compete with centers competing in their preterminal year next year. Additional program activities, such as the CLINFO project, will be funded in accordance with the results of the upcoming review this spring.

It is expected that approximately the same number of centers will be maintained although occupancy, beds and personnel will be reduced depending upon final budget figures and the rate of cost increases.

GENERAL CLINICAL RESEARCH CENTERS

HISTORY OF APPROPRIATIONS AND CEILINGS RECOMMENDED
BY THE NATIONAL ADVISORY RESEARCH RESOURCES COUNCIL

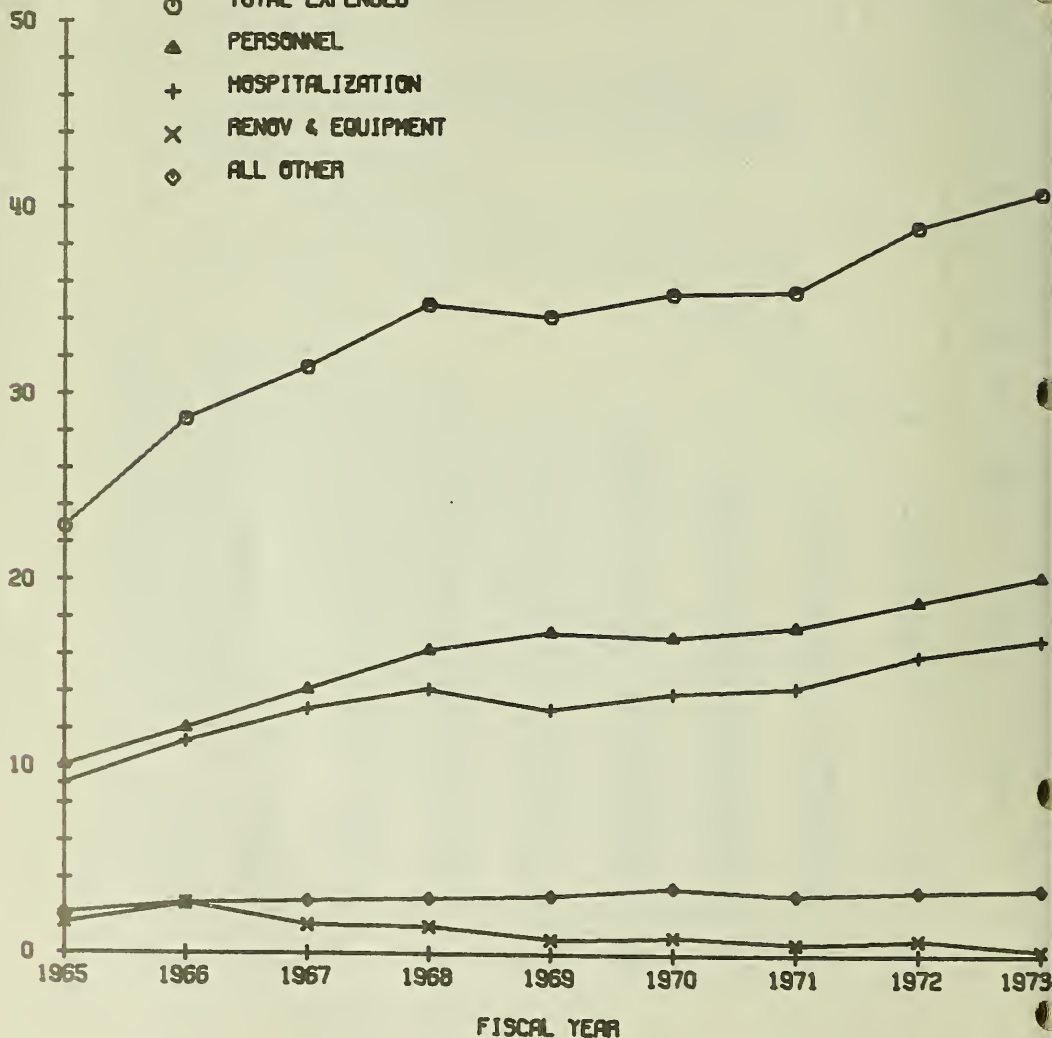
GENERAL CLINICAL RESEARCH CENTERS

HISTORY OF EXPENDITURES BY SELECTED BUDGET CATEGORIES

FISCAL YEARS 1965 - 1973

MILLIONS
OF DOLLARS

- TOTAL EXPENDED
- ▲ PERSONNEL
- + HOSPITALIZATION
- x RENOV & EQUIPMENT
- ◇ ALL OTHER



***INCLUDES AWARDED DATA FOR 32 AGC'S NOT YET RECEIVED

Fiscal Year 1974
Annual Report
General Research Support Branch
Division of Research Resources

The General Research Support Branch in FY 1974 administered the General Research Support Grant, the Biomedical Sciences Support Grant, the Health Sciences Advancement Award, and the Minority Biomedical Support programs.

GENERAL RESEARCH SUPPORT GRANT
AND
BIOMEDICAL SCIENCES SUPPORT GRANT
PROGRAMS

The General Research Support Grant (GRSG) program was initiated in 1962 after the passage of Public Law 86-798. GRSG funds are awarded for the general support of health-related research activities to medical and other health professional schools, hospitals, and other non-academic research institutions. In 1966, the companion Biomedical Sciences Support Grant (BSSG) program was initiated. This program is conceptually identical to the GRSG program, but provides funds to academic institutions other than health professional schools.

The GRSG/BSSG programs complement the NIH and NIMH categorical program grants by providing self-determined flexible short-term support for purposes such as pilot projects, central and shared equipment and facilities, new investigators, unexpected and emergency needs of projects supported by categorical programs, maintenance and enhancement of investigators' biomedical research skills, new and more effective patterns of use of facilities and equipment, preliminary investigations in new fields and fields new to an investigator, development of departmental and interdepartmental programs responsive to new biomedical science needs, support of affirmative action plans to involve minority persons in biomedical research, and support of compliance with animal welfare requirements. Some of these needs frequently require relatively small amounts of funds that do not justify incurring the overhead costs of central NIH review, some are multicategorical and therefore unsuitable for categorical support, some require quick response if the opportunity is to be grasped or costly delays to be avoided, and all represent important contribution to the goals of optimal effectiveness and efficiency of the national biomedical research effort.

Table I shows how GRSG funds were used in FY 1972.

TABLE I

FY 1972 Expenditure of General Research Support Grant Funds by Activity

	<u>Number</u>	<u>Dollars (in thousands)</u>	<u>% of Total Dollars</u>
RESEARCH PROJECTS	<u>7,778</u>		
New Pilot Proj.	1,604	\$ 4,398	9.9
Cont. Pilot Proj.	1,276	3,914	8.8
New Reg. Res. Proj.	1,513	6,087	13.7
Cont. Reg. Res. Proj.	3,385	15,617	35.3
CENTRAL RESOURCES			
Animal Facilities		2,282	5.2
Computer Facility		1,646	3.7
General Use Equip.		1,585	3.6
Instrument Shop		542	1.2
Central Lab. Facility		1,932	4.4
Photog. and Med. Arts		335	0.8
Other		2,290	5.2
RESEARCH TRAINING		2,342	5.3
OTHER ACTIVITIES		<u>1,313</u>	<u>2.9</u>
Total		\$44,283	100.0

Fiscal and Administrative Considerations

During FY 1974, FY 1973 impounded funds were released; \$29,043,000 for the GRSG program and \$4,533,000 for the BSSG program. Supplemental FY 1973 awards were made to 327 GRSG and 117 BSSG institutions. In addition, \$38,225,000 was awarded to GRSG institutions and \$6,007,000 to BSSG institutions from FY 1974 funds. Tables II and III show for the GRSG and BSSG programs respectively, (1) the trend in allowable research grants awarded by NIH and NIMH to eligible GRSG or BSSG institutions (entitlement) since the initiation of the programs, (2) the trend in award funds, and (3) the relation between entitlement and awards.

TABLE II

GENERAL RESEARCH SUPPORT GRANT PROGRAM
Trends in NIH/NIMH Research Grant Awards

(Entitlements) 1/ and in General Research Support Grant Funds, FY 1962-1974

Fiscal Year	NIH/NIMH Awards (Entitlement)	GRSG Funds Awarded	Ratio (%) GRSG/Entitlement
1962	\$108,234,000	\$20,000,000	18.48%
1963	192,408,000	30,000,000	15.59
1964	241,426,000	35,000,000	14.50
1965	286,832,935	43,985,365	15.33
1966	320,415,167	39,200,000	12.23
1967	354,893,188	41,700,000	11.75
1968	393,366,592	48,174,445	12.25
1969	441,064,040	48,200,000	10.93
1970	448,080,707	45,802,000	10.22
1971	430,721,426	43,423,000	10.08
1972	495,806,184	44,298,000	8.93
1973	577,966,843	46,277,000 <u>2/</u>	8.00
1974	667,273,190	38,225,000	5.73

1/ Previous Fiscal Year Awards Received From the NIH Institutes and NIMH by GRSG Awardees.

2/ Includes \$29,043,000 released impounded funds awarded as 1973 supplements.

TABLE III

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM
Trends in NIH/NIMH Research Grant Awards
(Entitlements) and in BSSG Funds, FY 1966-1974 1/

Fiscal Year	NIH/NIMH Awards (Entitlement)	BSSG Funds Awarded	Ratio (%) BSSG/Entitlement
1966	\$ 80,233,656	\$ 5,000,000	6.23%
1967	87,564,767	6,000,000	6.85
1968	108,925,527	7,500,000	6.89
1969	119,007,903	7,500,000	6.30
1970	123,150,660	7,125,000	5.79
1971	122,385,049	6,777,000	5.54
1972	138,129,124	6,914,000	5.01
1973	160,949,957	7,223,000 <u>2/</u>	4.48
1974	174,303,033	6,007,000	3.45

1/ Previous Fiscal Year Awards Received From the NIH Institutes and NIMH by BSSG Awardees.

2/ Includes \$4,533,000 released impounded funds awarded as 1973 supplements.

It was planned to merge the GRSG/BSSG programs into one program in FY 1974, but due to the uncertainty of the future status of funding, the GRSG/BSSG programs were not merged and were administered in accordance with the policies which governed FY 1973 awards, including eligibility requirements. Approximately the same number of institutions received GRSG/BSSG awards as in FY 1973 but at a greatly reduced funding level, as shown in Tables IV, V and VI below.

TABLE IV

GENERAL RESEARCH SUPPORT GRANT PROGRAM

Number of Grantees by Type for the General Research
Support Grant Program FY 1967 - 1974

Type of Grantee Inst.	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974 ^{1/}
Medicine	90	95	99	100	100	101	104	104
Dentistry	49	49	49	49	33	34	34	30
Osteopathy	5	5	5	5	0	0	0	0
Pub. Health	12	12	12	12	12	12	12	12
Pharmacy	9	10	12	15	15	16	14	12
Vet. Med.	13	15	17	17	17	16	15	14
Nursing	0	0	0	0	2	4	3	3
Allied Health	0	0	0	0	0	0	1	1
Hospitals	64	71	75	79	76	79	71	66
Health Dept.	3	3	3	3	2	2	2	2
Res. Inst.	49	51	58	64	69	75	71	70
TOTAL	294	311	330	344	326	339	327	314

^{1/} Estimated. Final awards have not been made.

TABLE V

GENERAL RESEARCH SUPPORT GRANT PROGRAM
Distribution of General Research Support Grants by Size of Awards
and Funds Awarded for Fiscal Years 1967 Through 1974

Size of Grant (in thousands)	Number of Institutions							
	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY ^{1/} 1974
Under - \$ 30.0	22	27	30	49	34	46	17	42
\$ 30 - 49.9	58	54	46	47	51	54	67	64
50 - 99.9	60	74	80	85	77	78	69	68
100 - 149.9	36	41	49	41	50	36	41	48
150 - 199.9	40	40	36	34	36	45	41	45
200 - 249.9	26	21	21	26	25	26	36	15
250 - 299.9	17	19	29	31	25	21	19	32
300 - 349.9	14	13	12	8	8	10	12	---
350 - 399.9	9	13	9	23	20	23	25	---
400 - 449.9	12	9	18	---	---	---	---	---
450 - 499.9	---	---	---	---	---	---	---	---
500 - 599.9	---	---	---	---	---	---	---	---
TOTAL	294	311	330	344	326	339	327	314

Grant Range (All Inst.)	Amounts (In Thousands)							
	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY ^{1/} 1974
Low	\$ 14	13	12	5	11	12	11	14
High	441	424	429	396	383	367	359	252
Average	142	155	146	133	133	130	141	106

Total General Research Support Grant Funds Awarded (In Millions)

	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974
Total Funds Awarded	\$41.7	\$48.2	\$48.2	\$45.8	\$43.4	\$44.3	\$46.2	^{2/} \$38.2

^{1/} Estimated. Final awards have not been made.

^{2/} Includes \$29.0 (millions) released impounded funds.

TABLE VI

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM

Distribution of Biomedical Sciences Support Grants by Size of Awards
and Funds Awarded for Fiscal Years 1967 Through 1974

Size of Grants (In thousands)	Number of Institutions							
	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974
Under - \$ 30.0	-	-	1	8	8	14	7	16
\$ 30 - 49.9	32	27	36	35	36	36	38	42
50 - 99.9	54	60	59	59	57	59	53	45
100 - 149.9	6	11	11	9	9	5	11	1
150 - 199.9	1	3	2	2	1	2	2	4
200 - 249.9	-	1	1	-	1	1	2	--
Total No. of Grants	93	102	110	113	112	117	113	108

Grant Range (All Inst.)	Amounts (in thousands)							
	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974
Low	\$ 33	\$ 36	\$ 29	\$ 15	\$ 12	\$ 15	\$ 27	\$ 23
High	179	219	220	199	210	212	221	187
Average	65	74	68	63	61	59	63	56

Total Biomedical Sciences Support Grant Funds Awarded (In Millions)

	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974
Total Funds Awarded	\$6.0	\$7.5	\$7.5	\$7.1	\$6.7	\$6.9	\$7.2 ^{1/}	\$6.0

^{1/} Includes \$4.5 (millions) released impounded funds.

Numerous Congressional and grantee institution letters were received concerning the problems that the uncertain GRSG/BSSG budget for FY 1973, 1974 and 1975 is having on institution planning. The original FY 1973 GRSG/BSSG allocation was \$19,924,000. Released impounded funds added \$33,576,000. The President's budget for FY 1974 called for \$9,500,000, but the final allocation was \$44,232,000. The President's budget for FY 1975 requested no funds for the GRSG/BSSG program. It has been very difficult for an institution to plan with the uncertainties of the GRSG/BSSG budgets.

GRSG/BSSG Program Plans 1975

The General Research Support Program Advisory Committee and Staff of the Division of Research Resources will continue efforts underway in FY 1974 to determine steps that should be taken to keep the GRSG/BSSG programs responsive to changing needs and opportunities, including the newly adopted contemporary objective for DRR.

Although the Administration's fiscal year 1975 budget requests no appropriation for GRSG/BSSG because other biomedical research programs were judged to have a higher priority and choices were made in seeking to achieve expenditure goals for 1975, it is prudent to continue work on the issues that confront GRSG/BSSG because the details of the 1975 appropriation that ultimately will be enacted cannot be foreseen, and because budgetary constraints may be eased so that support for these valuable programs can be resumed without prolonged delay. Issues being addressed include usage of funds, eligibility criteria, determination of award amounts, merger of GRSG and BSSG programs, and reporting and accountability by grantees.

HEALTH SCIENCES ADVANCEMENT AWARD PROGRAM

The moratorium on new applications for Health Sciences Advancement Awards resulted in complete phase out of the program in FY 1974. During FY 1974 the final two non-competing continuation awards were made to the following:

University of Kansas
Duke University

During FY 1975 it is planned to have an evaluation made of the Health Sciences Advancement Award program.

MINORITY BIOMEDICAL SUPPORT PROGRAM

The Minority Biomedical Support (MBS) program started in FY 1972 by the Division of Research Resources was designed to strengthen the institutional health-related research capabilities of four-year colleges, universities and health professional schools in which student enrollments are drawn mainly from ethnic minority groups. It constitutes the major focus and concentrated effort of the NIH to involve minority institution scientists in biomedical research and to expose minority students to the challenges and opportunities in biomedicine.

This program was initiated, at the encouragement of the Senate Appropriations Committee, in order that minority groups may have equality of opportunity to become investigators in biomedical research.

Since the MBS program was modeled after no other program within NIH, it is unique and therefore has been experimental and changing in nature. Consequently, the program has been improved as need for modification has been gained through experience.

The goal of the MBS program is to increase the number of ethnic minority individuals in the biomedical sciences by developing and improving opportunities for biomedical research and research participation of ethnic minority faculty, students and other investigators, and by assisting in the provision of appropriate settings conducive to these opportunities.

During FY 1974 the program was gradually modified to include four-year colleges where there are large numbers of minority (i.e., Black, Spanish-speaking, American Indian, or Oriental) students, but not necessarily a majority (as required under the original MBS program guidelines.) There are also a few junior colleges and community colleges where there are large numbers of minority students enrolled. By including these institutions and others such as the American Indian Tribal Councils, the program could reach a considerable number of minorities, including Spanish-speaking people and American Indians, as well as many Blacks, who were originally excluded from the program. The desirability and feasibility of such changes in institutional eligibility is being closely followed.

Program Data and Fiscal Considerations

Table VII below shows the number of awards and amount funded since the MBS program was initiated in FY 1972. The President's budget requests \$7,270,000 in FY 1975; a decrease of \$730,000 from that awarded in FY 1973. Currently 66 MBS grants are supporting 72 institutions.

TABLE VII
MINORITY BIOMEDICAL SUPPORT AWARDS

<u>Type</u>	<u>FY 1972</u>	
	<u>Number Awarded</u>	<u>Amount Funded</u>
New	38	\$ 2,000,000
<u>Type</u>	<u>FY 1973</u>	
	<u>Number Awarded</u>	<u>Amount Funded</u>
New	14	\$ 968,551
Renewal	1	54,947
Continuation	<u>36</u>	<u>3,976,502</u>
	51	\$ 5,000,000
<u>Type</u>	<u>FY 1974</u>	
	<u>Number Awarded</u>	<u>Amount Funded</u>
New	15	\$ 1,806,128 ^{1/}
Competing Supplements	13	774,325
Continuation	<u>51</u>	<u>5,419,547</u>
	79	\$ 8,000,000

^{1/} Includes 8 eighteen-month awards made from \$1,000,000 FY 1973 released impounded funds.

Table VIII below shows the predominant minorities being supported at the 72 institutions receiving MBS support.

TABLE VIII

Minority Biomedical Support Program

Predominant Minorities at 72 Institutions
Being Supported by MBS Awards

	<u>Institutions</u>
Black	54
Spanish-speaking	13
Hawaiian	2
American Indian	<u>3</u>
	72

Table IX below shows the faculty and student support since the MBS program was initiated in FY 1972. There has been an increase of 150 percent in faculty support, 215 percent in undergraduate student support, 225 percent in graduate student support, and 100 percent in postdoctoral support between FY 1972 and FY 1974.

TABLE IX

Faculty and Student Support
from
Minority Biomedical Support Awards

	<u>Faculty</u>	<u>Undergraduate Participation</u>	<u>Graduate Participation</u>	<u>Postdoctoral Participation</u>	<u>Total</u>
1972	199	288	44	1	532
1973	358	643	94		1,095
1974	499	906	143	2	1,550

Several MBS grantees have strongly requested that indirect cost payments be allowed. Indirect cost payments are not paid because the annual appropriation act states that "..... none of these funds shall be used to pay recipients of the general research support grant programs any amount for indirect expenses in connection with such grants." The MBS program is under the authorizing legislation for general research support (Section 301 [d], Public Health Service Act, Amended). It is estimated that an additional 30 percent in funding would be required in FY 1975 if indirect costs were authorized. Because of commitments this increase could not be absorbed.

Projects being supported by the MBS Program include such diverse areas as the following:

"Chromosome Specificity of Incorporated Exogenous DNA."
(Tuskegee Institute)

"Sequencing of Peptides Using Negative Ion Mass Spectrometry."
(California State University, Los Angeles)

"A Clinical Study of Acute Myocardial Infarction in Black Americans."
(Howard University)

"The Effect of Prostaglandins on Ploidy Distribution in Rat Liver."
(Albany State College, Albany, Ga.)

"Eukaryotic Transcription by RNA Polymerase."
(Atlanta University)

"Morphine Addiction: Instrumental Behavior and the Hypothalamus."
(Jackson State College)

In April 1974, students and faculty presented 73 papers in biological sciences, 24 in biochemistry, 36 in chemistry, and 12 in pharmacology at the Annual Xavier University MBS Symposium in New Orleans. Additionally, students and faculty have presented papers at regional AAAS, ACS, Society of Microbiologists, and other meetings in the past year. At least two of the student papers presented in meetings of Beta Kappa Chi have received cash awards for the best paper presented at the meeting.

Investigators have already submitted papers for publication in scientific journals; some have already submitted grant applications to NIH and other research granting agencies and have received funding.

Fiscal Year 1974 Annual Report
Program Analysis Branch
Division of Research Resources

The Program Analysis Branch is responsible for continually assessing the Division's data requirements and structuring an appropriate Division-wide data base. This includes aspects of system analysis and design attendant to establishing a system, maintenance of data in the systems and use of the systems to produce the required output, including the project planning and programming functions. Some of the Program Analysis Branch efforts initiated during the past year to meet the Division's requirements for data reporting and program evaluation have been:

1. A program was written and catalogued to edit the GRSG and BSSG expenditures and annual progress report data. Before automation, this function was done manually by the General Research Support Branch staff.
2. A system for the collection of data on the Minority Biomedical Support Program is being developed. The first phase -- awards and expenditures data -- has been implemented. Further discussions are planned regarding the scientific research project, trainee and personnel supported data before a procedure is established. This will be accomplished within the next few months.
3. The Biotechnology Resources data system was expanded to include the budget operating levels of the grantees, as well as the expenditure data reported in the Progress Report. A masterfile of the research projects was designed and implemented on a test basis.
4. The scientific data for fiscal year 1971 GRS and BSS grants were collected. Because of the uncertainty of these two programs and the large volume of work, this project has been temporarily discontinued.
5. The General Clinical Research Centers data items on the master file were redesigned to include NARRC budget and personnel recommendations. Programs have been written to produce several reports previously prepared by hand.

FAB provides computation services for the GRS and BSS grant awards by performing the tasks associated with the calculation and award of these grants. FAB has developed and is responsible for an intricate series of computer programs and subroutines which apply a multiple set of conditions to an institution's entitlement, calculate the amount of the award, punch the cards used to prepare the award statement by computer and produce listings and tables of the relevant data. When the need arises, FAB adapts these programs and subroutines to produce experimental manipulation of the GRS and BSS data in order to analyze the effect of various alterations of the formula and the resulting impact on the GRS and BSS programs. In the past year, the Branch calculated a vast array of experimental awards to

assist the GRS staff in redesigning the GRS and BSS awards program in this regard.

PAB is still developing a "Division of Research Resources Basic Data Book" which will be a collection of highlighted DRR data and related facts in a pocket-size booklet. Considerable historical tabular data has been compacted into various creative displays to experiment with and select those which will be most communicative and useful to the Division.

The PAB continues to assist the General Clinical Research Centers Branch in establishing criteria and processing appropriate data to be used in evaluating characteristics and effectiveness of the center's program, even though the formal evaluation study has concluded.

The Branch has supported the program planning activities of NIH by assisting in the development of an evaluative study for the Institutional Profile Subcommittee of the Center Grants Task Force. Data was queried from DRG and many lists produced for review. Many different samples were prepared. Considerable time and energy has been spent in developing the methodology to obtain the necessary data and designing strategies and techniques for surveying grantee institutions.

The data system established by PAB for the Division contains approximately 309 data items which are defined and described in the PAB Handbook of Definitions and Specifications for the three distinct master files maintained, as well as in the documentation for the Publication Retrieval System master files. A completely computerized system has been established and, depending on the nature of the task, access to the data is accomplished through the 360/20 remote or the IBM 2741 Communication Terminal. Various methods are used such as computer programs, the Inquiry and Reporting System (IRS), and the Publications Retrieval System (PRS).

The source documents for these data are grant applications, award statements, expenditures reports and annual reports submitted by grantees. From this data bank, PAB produces annual and periodic publications such as:

1. The "Research Resource Grants" booklet which contains highlights, graphs, highlight tables, summary tables and listings that pertain to the DRR grants and that reflect the magnitude, scientific and technical diversity, geographical coverage, and general vitality of these programs of support for resources.
2. A publication for the National Advisory Research Resources Council, "Division of Research Resources Handbook," which is a compendium of current and historical data on the appropriations and awards of the Division and its four programs, and which presents a brief description of the goals, objectives and general activities of the Division's programs.
3. The General Research Support Program Awards History Booklet which lists the name, location, type of institution, grant number and amount of award for each recipient of general research support since the

inception of the program in 1962, and includes summary tables by type of institution within fiscal year and by geographic division within fiscal year.

4. A Biomedical Sciences Support Program Awards History Booklet which contains the same type of information for this program as described under (3) for the GRS program.

5. The General Research Support Expenditures Booklet which shows the data over a six-year span as tabulated from the Annual Report of Expenditures filed by all recipients of General Research Support; the booklet includes summary tables for all types of institutions according to the type.

6. A Biomedical Sciences Support Program Expenditures Booklet similarly constructed as that described in (5) above.

In addition, the Branch has responded to inquiries for data maintained by DRG. PAB has written queries to obtain on a regular basis such information as active NIH research grant support at selected institutions, grants with \$10,000 or more awarded for Hospitalization, and NIH grant support using vertebrate animals. The CRISP files were accessed to obtain information on grants using marine invertebrates and those doing research on sleep disorders.

The above exemplify some of the Program Analysis Branch's efforts to meet the Division's requirements for data reporting and program evaluation as they fit into the decision making process. During the coming year PAB will continue to study the Branches' data needs in order to expand its data base for analysis. Future plans include

1. - expanding the MBS data base to collect the scientific and trainee data;
2. - establishing a procedure to analyze and link DRR resource user's to other components of NIH.

Office of Science and Health Reports

"'How Children Grow,' published by the National Institutes of Health, explains what research scientists have been learning about growth and development of children. Included is a chapter on adolescent obesity. Single copies are free from. . ."

National Observer article
by Daniel Henninger

"From my review of the publication, it was apparent that it follows closely the course outline and content of the 'Human Behavior and the Social Environment Course' and would be a vital and useful tool to students in the class."

letter from Daniel R. Rubenstein, Ph.D.
Chairperson, Dept. of Social Work
West Virginia College of Graduate Studies

"I have reviewed it, and feel it would be most suitable for our course on growth and development."

letter from Theresa A. Hudak, R.N.
New Ulm School of Practical Nursing, Minn.

"I have found the booklet an excellent source for the teaching of students and an excellent reference for future careers; consequently, I wonder if it would be possible to obtain 200 copies which I can distribute to the students in my class. . ."

letter from Norman Kretchner, M.D., Ph.D.
Faber Professor of Pediatrics
Director, Section of Developmental Medicine
Stanford University Medical Center
new Director of NICHD

From all across America, professionals and plain citizens alike wrote to request copies of DRR publications. In calendar year 1973, the Office of Science and Health Reports received almost 59,000 individual requests for material. The majority of this varied audience requested "How Children Grow," confirming the strong effect of continued communications activities by the Office involving the booklet.

During the fiscal year, "The Family Economist," published by the Insurance Institute of America carried a major feature article on "How Children Grow," which they mailed to over 1,400 editors throughout the United States. "Child Development Abstracts and Bibliography" of the Society for Research in Child Development published an abstract complimentary of the publication. The National Observer recommended it to its readers, and House and Garden carried the message to its 1 million readers. Women's Circle magazine and FREE AND INEXPENSIVE LEARNING MATERIALS published by George Peabody College of Teachers both featured it. The publication was reviewed and recommended by the Journal

of Nutrition Education, which called it an "excellent reference for nutrition educators, parents, teachers, and many others concerned about children's welfare." The Day Care and Child Development Council of America reprinted the publication in its entirety. This organization noted that "How Children Grow" contained "excellent information which can be of great use for those who are training staff to work with young children." Individual citizens wrote letters of praise. A mother in Plaster City, California, told the Office: "'How Children Grow' has answered many questions that had been troubling me, and it now has a permanent place on my book shelf." A lecturer in the Growth Sciences Division, College for Human Development, Syracuse University, wrote: "I intend to emphasize the book as a resource for students in working with children and their parents in nursery and elementary schools." The Coordinator of Parents Classes at Washington's Columbia Hospital for Women complimented the Division on the excellence of its publication. Throughout the year, parents, directors of day care facilities, dietitians, nutritionists, pediatric nurses, medical students, public health nurses, pediatricians, child psychology students, and educators praised the booklet and requested it for their use.

During the year, the Office developed, wrote, and published a new folder titled "Do We Care About Research Animals?," which quickly became popular. The National Society for Medical Research featured it in their newsletter and requested 3,000 copies for distribution to interested persons. The Assistant Director of Scientific Activities of the American Veterinary Medical Association called it an "excellent new folder." A teacher at State University of New York wrote: "As an instructor of veterinary science one of the biggest problems I have is that of 'emotional-reactive' students toward the use of laboratory animals, whether it be for vivisection, injection instruction, intraorbital bleeding, and on, and on. Would it be possible for you to send me an additional 150 copies of the above publication. I believe it would greatly benefit in explaining what we are doing."

The Director of Public Relations at Duke University Medical Center requested copies to counter public criticism that resulted from a newspaper story on research animal facilities at Duke.

The American Association for Laboratory Animal Science featured the folder in its bulletin. People across the country began writing AALAS for copies, after prints of a one-minute television spot, which the Office of Science and Health Reports had helped to develop in conjunction with AALAS, began to appear on local television stations.

The National Society for Medical Research sent the new folder individually to all members of Congress. Senators Stafford, Eastland, Taft, Bayh, Abourezk, and Beall and Congressmen Patten, Stafford, Young, Mizell, Whitehurst, Davis, Casey, and Congresswoman Holtzman wrote NSMR to thank them and to order additional copies.

In an unusual move, The Frederick Post reprinted the entire folder on its editorial page under the headline "NIH Cares About Animals."

In other activities, a television documentary which was an office project had a repeat showing over hundreds of TV stations of the ABC network. On August 9, "How To Stay Alive" brought dozens of news clips which were directly connected with the Office's activities. Publicity appeared in many newspapers, including the Richmond Times Dispatch, Buffalo Evening News, Syracuse Herald Journal, Cleveland Press, and the Atlanta Journal.

As part of the show, the Office of Science and Health Reports made arrangements for the Chief of the General Clinical Research Centers Branch to appear for a second time in a short filmed segment. He appeared in other portions of the hour.

The NIH's clinical research centers received billing next to the main title of the special. As participants, each of the Division's grantee program director experts and his institution received additional billing. At the end of the special, the Division received full credits.

A major story on ambulatory centers, an offshoot of the General Clinical Research Centers Program, appeared in Laboratory Management. The piece was written and photographed by the Office. It told the story of the emerging outpatient clinical research centers at Vanderbilt University Medical Center in Nashville, Tennessee.

Ron Maselka of the Buffalo Evening News wrote a number of articles about the National Institutes of Health. Recently, in an effort to tell more about itself, the NIH reprinted these articles in booklet form. The Office had worked very closely with the correspondent on two of the articles featuring DRR programs among the 13 that were reprinted. These covered animal resources and clinical research centers. In addition, the Office furnished background information for a Maselka story during the year on a group of Buffalo medical researchers. They were becoming a part of the Division's pharmacology and toxicology computerized information system known as PROPHEET. This piece used extensive quotes by the Chief of the Biotechnology Resources Branch as he described the program.

The PROPHEET System was also the subject of articles in Chemical and Engineering News and the Federation Proceedings published by the Federation of American Societies for Experimental Biology. Both articles emphasized quotes from the Branch Chief. They described in detail the inner workings of this innovative approach to pharmacology/toxicology research and heralded the use of advanced information science tools in biomedical research.

The Office of Science and Health Reports originated and placed articles and pictures on the degu, the rat-like animal with two thymus glands, in Medical Tribune, Children Today, Lab Animal, Federation Proceedings, ILAR News (in which it was the cover story), and DVM, the veterinary medicine magazine.

Operating in close cooperation with Xavier University of New Orleans which provided pictures and some background, the Office produced a news story with photos on the Second Annual Xavier-Minority Biomedical Support Symposium. These went to a representative minority press list throughout the United States. Arrangements were made for an article on the MBS Program written by the Office

to appear in the upcoming special September education issue of FASEB's Federation Proceedings, together with pictures.

Earlier in the year, a feature news article on MBS was written and mailed to black weekly papers. Among the users were the Iowa Bystander, the Monroe, La., News Leader, and the Twin Cities Courier.

The Office produced a heavily illustrated booklet on the UCLA Health Sciences Computing Facility for the Biotechnology Resources Branch. Working closely with the staff at UCLA, the Office covered the activities of the center, wrote the narrative for the booklet, developed layout and dummy, and checked these with the scientists and administrators involved. A beautiful publication on this strongly-supported biotechnology resource resulted. As the fiscal year drew to a close, arrangements had been made to reprint a portion of the booklet in the Federation Proceedings, published by FASEB, and negotiations were proceeding on a major piece from the booklet for Government Data Systems. In addition, Enterprise Science News was showing interest, and news material and the booklet itself had been sent to all data and computer publications.

In the audiovisual area, the Office arranged for and set up the tabletop Primate Research Centers exhibit at the 1973 annual American Medical Writers Association in Bethesda. Cooperating with the Animal Resources Branch, assistance was also provided in running the ARB exhibit at the national convention of the American Association for Laboratory Animal Science in Bal Harbour.

During the year, a custom-built display was designed by the Office for use in emergency and temporary situations. This unit was used to advantage during the National Advisory Research Resources Council and the General Research Support Program Advisory Committee meetings in the spring.

In cooperation with the University of Alabama, the Office wrote a story on a Division-supported animal resource featuring cats with a disease similar to Tay-Sachs in humans. This story was widely carried in the Jewish press, including the Baltimore Jewish Times, the Jersey City Jewish Standard, the Buffalo Jewish Review, the Kansas City Jewish Chronicle, the Newark Jewish News, and the Philadelphia Jewish Exponent. Other papers ran the story, together with the Washington Star-News.

A news story developed by the Office about a shortage of nonhuman primates in biomedical research was run by Science magazine. Featuring extensive quotes from the Chief of the Primate Research Centers Section, the news story announced the start of a worldwide primate census of biomedically important animals. This survey was financed by the Animal Resources Branch and run by the Institute of Laboratory Animal Resources. In addition, the story was carried by Lab Animal, Drug Research Reports, the AALAS Bulletin, the Laboratory Primate Newsletter, and the Federation Proceedings. The Denver Post ran a major article on the problem of declining primate populations, which was sparked by the Science story. It gave extensive space to quotes from the Chief of the Primate Research Centers Section.

Two major articles were conceived, written, and illustrated for Lab Animal. The first piece was called "A New 'Hot' Lab for Primate Pathogens," and covered the special isolation facility at the Delta Primate Research Center. Though it was not photographed by the Office, photos were provided. The second article, "Manpower Development for Laboratory Animal Science" was devoted to a long interview with the Chief of the Animal Resources Branch on the program's new special training activities. Pictures were shot by the Office and provided with the interview to the bimonthly publication.

The Office also provided Lab Animal with tapes of two major NIH meetings which were co-sponsored by the Animal Resources Branch. Reports appeared in two consecutive issues on "Automated Animal Caging Systems" and "Bioprotective Caging Systems."

An in-depth report on marine invertebrates, which resulted from a meeting of 20 marine experts at NIH brought together by the Animal Resources Branch, appeared in the Federation Proceedings of FASEB. The meeting report, written by the Office, resulted in dozens of requests for reprints from all over the world.

"This particular species of beetle may become a more versatile insect model for the current frontiers in modern biology and biomedicine than Drosophila was for genetics," said Dr. Dale M. Norris in an Office-generated story about the wood-boring beetle. During the year, a feature story about this unique new animal model was used prominently by Lab Animal, the National Society for Medical Research Bulletin, the Federation Proceedings, and "Dateline Science" in Scholastic Magazine.

These various activities were selected to show the span of the Office's work during the year. This report does not address itself to the many individual placements and projects, too numerous to mention, in which the Office was involved.

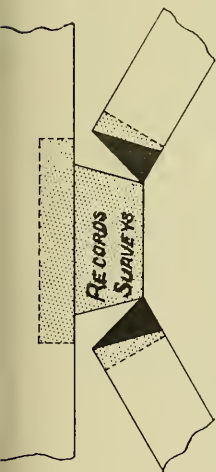
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HOW TO USE
THESE SEPARATORS

Use one page for
each separation.

Select appropriate
tab, add further
identification if
desired, and cover
it with scotch
tape.

Cut off and discard
all tabs except the
one covered by tape.



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DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1973 through June 30, 1974

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NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES -- DR. JOE R. HELD, DIRECTOR

Report of Program Activities
July 1, 1973, through June 30, 1974

A. Objectives

The Division of Research Services supports other NIH components by providing centralized scientific, technical, and engineering services essential to biomedical research. Division programs function through a staff of professional and technical personnel organized into five Branches: Biomedical Engineering and Instrumentation, Environmental Services, Library, Medical Arts and Photography, and Veterinary Resources.

B. Current Programs

A broad range of central research support services and products are provided by the Division of Research Services. These currently include the following:

1. The application of engineering principles and techniques to the solution of biomedical problems.
2. The design, fabrication, and maintenance of special research instruments.
3. Environmental surveillance to detect and eliminate conditions adverse to conducting high quality research or hazardous to patients, employees, or the community.
4. Library and bibliographic services.
5. Foreign language translation.
6. Still photography and motion picture production.
7. Graphics arts services and exhibits design.
8. Medical illustration and model making.
9. Animal production, procurement, conditioning and holding.
10. Animal health services.
11. Experimental surgery and related activities.
12. The production of tissue cultures, microbiologic medias and animal biologics.
13. Central processing and sterile preparation of laboratory glassware.

C. Program Progress and Accomplishments

1. Biomedical Engineering and Instrumentation

Several major projects initiated and developed in preceding years matured and were reduced to practice. Mathmatically derived chemotherapeutic protocols were established for managing certain cancer cases. Pharmacodynamic principles were applied and achieved more optimal hemodialysis of patients suffering from renal failure.

Prototype clinical instrumentation systems based on video technology were accepted as practical tools for monitoring cardiac performance and the condition of aortic ball valve prostheses *in vivo*; noninvasive ultrasonic imaging for measurement of heart muscle dimensions has become relatively routine.

Previously developed concepts and equipment for investigating concussion were regularly used to generate and analyze reproducible data from head injury experiments. Formalized inspection and maintenance routines for patient care apparatus in the Clinical Center were implemented. The Scientific Equipment Rental Program was broadly accepted and used by a substantial portion of the NIH community as a reliable, economic resource and expanded markedly.

Investigations with substantial potential for future applications were initiated in several important areas, including the identification and assessment of trace metallic complexes in cancer therapy and environmental contamination, the interaction of implanted polymers with blood and body fluids, fluid mechanical influences on atherosclerotic plaque formation, ionic concomitants of cortical metabolism, faster and more sensitive microcalorimetry, and comprehensive instrumentation for investigating the behavioral effects of anti-epileptic drugs.

Demands for consultation and assistance with collaborative and extramural programs exceeded resources available, as did requests from other government agencies for fabrication of unique technical systems based upon BEIB designs and prototypes.

2. Environmental Services

The Environmental Services Branch devoted major program effort to assessment of chemical carcinogen hazards; procurement of laminar flow biological safety cabinets; and review of laboratory facilities working with potentially hazardous Class III, IV and "non-natural" organisms. The most notable review of laboratory facilities was in association with the NIAID for compliance with the "Memorandum of Understanding and Agreement" for the safe handling of Adenovirus Type 2 - SV40 Hybrids.

A survey of chemical carcinogen usage was initiated in response to tentative standards under the Occupational Safety and Health Act. Preliminary data provided basic information on chemical carcinogen use in research environments to the DHEW panel of experts formulated to develop standards. At NIH there are approximately 150 users of chemical carcinogens, 63 whom reported using one or more of the 14 designated chemical carcinogens of interest to the Department of Labor. An NIH program is now being formulated to deal with proper carcinogenic chemical identification, risk assessment, and control measures to be employed. Employee education will be included as a control measure.

Procurement of laminar flow biological safety cabinets at NIH reached a crisis point during the year because of unexpected demand for this safety

device--not only at NIH where it was developed, but in outside laboratories. Seventy-five new LFBSC's were put in use with approximately 100 more on order at the end of the fiscal year. The NIH specification for the cabinets was modified three times during the year. The Office of Materiel Management was informed by GSA late in the year that NIH could proceed with the development of a Qualified Products List for this equipment. The first LFBSC's constructed to NIH specifications were purchased during the year.

Pollution of the NIH stream on the Bethesda campus has apparently been brought under control, as the major contamination sources have been eliminated. Water pollution control activities at the National Institutes of Health Animal Center continued. The Sewage Treatment Plant experienced operational difficulties, as did the automatic water quality monitors. Noise control developed into a time-consuming program because of new Federal regulations. The chemical waste disposal program was developed to the point that the NIH treatment facility is under contract for renovation. A contract was initiated for disposal of chemicals which cannot be handled on NIH premises. The 870 chemical fume hoods were surveyed under contract to the DOW Chemical Company.

The contract to construct the Tri-Services Incinerator was cancelled and negotiations were begun with Montgomery County, Maryland, for the development of a Medical-Pathological Incinerator by the County to serve NIH and other medical research facilities within the County.

The training effort of the Branch was increased in several areas. A literature review entitled "Biological Laboratory Hazards" was developed and distributed quarterly to Laboratory and Department Chiefs at NIH. Approximately 150 research and technical staff of various institutes attended seminars on The Theory, Operation and Use of the Laminar Flow Biological Safety Cabinet. Of particular note was a cooperative effort with other NIH safety groups in the development of a series of safety posters and accompanying information in the NIH RECORD. An NIH sponsored short course on Introduction to Biological Laboratory Techniques was offered to summer employees. ESB personnel received 1,007 hours of training at designated short courses or classroom experience at local community colleges and universities. Three COSTEP trainees worked in the Branch.

3. Library Services

The suit of Williams and Wilkins Company against the Government for alleged copyright infringement relating to the photocopy service of the NIH Library and NLM and the copyright law was decided by the Court of Claims in favor of the Government in a four to three decision. The publishing company is appealing the Court of Claims decision to the Supreme Court.

The monthly listing of books, journals, and other literature added to the Library's collection is now issued as a memorandum from the Librarian. Translated articles are also listed.

A Scope and Coverage Committee was appointed to draw up a plan of action to formulate a Library policy for scope and coverage of literature acquired for the Library Collection. The first step, delineation of current B/I/D research and administrative needs through analysis of published programs, was completed.

Site surveys of automated circulation procedures in area libraries and literature studies were made by Library staff.

The Library participated in the NIH celebration of Black History and Native American Weeks. The Brancy Chief, a member of the NIH Minority Cultural Program Committee, served as a session Mistress of Ceremonies during Black History Week. Exhibits prepared by Library staff for each program were displayed in the outside corridor. High school students participating in the programs were given tours of the Library.

4. Medical Arts and Photography Services

Demands for MAPB services remained high. With a completely renovated Photo Lab, requests were serviced within five days and the Branch is committed to the reduction to seven days for photomicrograph and photomacrograph services by the end of FY 1975. The newly named and reorganized Design Graphics Section cut production 10 percent in reprint material, however, design and delivery of exhibits increased 100 percent. Medical Illustration continues a substantial steady output. MAPB increased its use of outside contract services by 26 percent. With new equipment and facilities, the Branch continued to improve and broaden its skills to meet increased program demands.

5. Veterinary Resources

A Catalogue of NIH Rodents was published. Characteristics of more than 100 strains and stocks of rodents and rabbits maintained in the VRB genetic repository are described in loose-leaf notebook form. Approximately 150 breeding nuclei of VRB strains of mice were provided to the international biomedical research community.

Investigators' requirements for VRB produced rodents and rabbits increased and total issues remained at about 500,000 despite a reduction in permanent personnel; however, an imbalance of temporary employees was utilized in some areas to maintain adequate production levels. Issues of noninbred animals from contract sources decreased.

The importance of maintaining the genetic pool of VRB noninbred stocks was demonstrated to be essential for the continuance of effective testing of biologicals. VRB colonies of mice now originate from hysterectomy-derived barrier-maintained breeding stock. New pathogen-free colonies were established this year and the old conventional colonies phased out.

While rodent, rabbit, and cat production dropped, laboratory reared dogs, timed-pregnant nonhuman primates, and ungulate production increased. Contracts were used to supplement canine, primate, and ungulate production as well as rodent production.

Cutbacks in rhesus monkey exports from India in 1974 prompted VRB to initiate domestic breeding programs. A new facility at Perrine, Florida, was obtained from the Environmental Protection Agency and is being stocked with over 700 rhesus breeders. Contracts are also being negotiated to initiate other domestic breeding colonies to produce 500 or more rhesus monkeys per year for use in NIH intramural research.

Experimental animal holding for dogs, which has long been over capacity, was, in part, contracted. With the Phase I renovation of Building 14D, protected facilities are available for holding 1,000 nonhuman primates. Over 1,700 primates will be held in this building on completion of Phase II and III renovations.

The Animal Disease Investigation Service was reorganized to insure rapid response to requests. The number of calls made to the BID has increased by 22 percent, from 150 to 183. They involved consultative, diagnostic, and therapeutic activities and included rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls also varied and involved all Institutes. This service, well received by the BID investigators, has gradually increased in scope. It has been mutually beneficial to investigators and to the VRB professional staff in providing an overview of laboratory animal facilities and practices at NIH.

D. Division Management

1. Personnel Appointments

Mrs. Jacqueline Waters, formerly with the Veterans Administration, was appointed Division Training Officer replacing Mr. James Byrne who transferred to the Department of Interior.

Mr. Charles Gensheimer joined the Personnel Management Specialist staff.

A key position, EEO Technician, was created during the year and Mr. Arthur Parks was recruited to broaden and strengthen the Division-wide EEO program.

A reexamination of the management analysis functions of the OD resulted in recruitment of Mr. Newell Quinton for manpower measurement and utilization studies throughout the organization.

2. Equal Employment Opportunity

The Division Human Relations Committee (HRC) continued to play a major role in channeling significant employee concerns to the Director. An EEO Seminar, the first in two years, was held in May to enhance awareness and understanding of aspects of the EEO program which tended to be overshadowed by problems of minority groups. The Seminar provided an opportunity to focus attention on attitudes toward reverse discrimination and sex discrimination. The HRC developed a quarterly report which will highlight significant accomplishments in EEO during the year. This report will be distributed throughout the Division to upgrade employee-management communications.

The creation of an EEO Technician position provides much needed assistance to the Division's EEO Coordinator and establishes a focal point for human relations problems at the GS-7 employee level or lower.

3. Employee Development

A selected group of approximately 60 key supervisory and administrative personnel participated in a two-day experiential laboratory to gain greater awareness of how individuals communicate with each other. In a similar effort, the Veterinary Resources Branch provided an opportunity for all supervisory personnel to attend a thirty-hour Leader Effectiveness course. In each instance, a major objective was to improve understanding of the importance of listening and its impact on the communications process.

DRS personnel continued to actively participate in the Adult Education and Upward Mobility College programs. It is anticipated that enrollment, particularly in the General Education Development program, will increase as employees become more involved in establishing career goals.

4. Training

A new direction in DRS training places emphasis on providing courses and programs to meet not only the functional needs of the Division but also to play a role in the long-range career development of the individual. To promote efficiency within the Training Office and to provide continued guidance for DRS personnel, career development folders are being established. When completed, these will present a complete training history for each employee.

Other plans for training include an internal program for on-the-job and Division orientation, supervisory training sessions geared to the specific needs of the participants, and a formal evaluation system to determine quality, feasibility, and effectiveness of training received by DRS personnel.

5. Management Analysis Projects

Personnel from the Division's Biomedical and Instrumentation Branch and the OD Management Analysis staff participated in an ongoing NIH-wide Materiel Management System study awarded to Arthur Young & Company. This study would coordinate inventory management, materiel flow, and financial accounting in all inventory systems with direct impact on the procedures used to collect cost and sales data in BEIB.

The Management Analysis staff initiated an extensive study of the flow of management information at all supervisory levels of the Division. The Data Reporting System, installed four years ago, is being critically reviewed in terms of its responsiveness to management's needs. Recurring ADP responsibilities at the OD level are being phased into the NIH support activities of the Division of Computer Research and Technology. The objective of the latter is to redirect existing systems analysis manpower from

routine EDP/ADP functions to broader work measurement and manpower utilization surveys throughout DRS.

6. Personnel Management

In cooperation with the Division EEO Coordinator, the Personnel office initiated a placement follow-up program for DRS. The personnel generalist and EEO Coordinator or technician met with each new Division employee 90 days after entrance on duty. The objective is to make employee orientation more effective and promote better communications on Division and NIH-wide matters.

Personnel and EEO staff met with supervisory personnel at all levels to enhance understanding of the annual performance appraisal system. The meaning of specific adjectives used in the rating system were clarified resulting in a more objective approach to employee appraisals.

The promotion review program, initiated in 1973, was continued and established as an annual procedure. Through this mechanism, the potential of every employee is reviewed in terms of his or her career goals as related to feasibility of advancement within the organization.

The Personnel Management staff participated extensively in the acquisition and staffing of a primate breeding facility in Perrine, Florida. Working closely with Environmental Protection Agency officials, DRS personnel staff was effected a smooth transfer and transition of Perrine employees to the NIH.

E. Visual Communications Projects

The Visual Communications Project Officer provided consultation and advice on a wide variety of visual and editorial design projects. Included were design and refurbishing of conference rooms for more effective visual presentation in the Office of the Director, NIH and the Director, National Cancer Institute. Consultation was also provided on graphic presentation in the conference room of the Director, National Heart and Lung Institute and on briefing materials for presenting research programs in other Institutes.

Work continued on the NCI series of slide/tape biohazard control and safety training packages. Two additional presentations were completed, "Selecting a Laminar Flow Biological Safety Cabinet" and "Decontamination of a Laminar Flow Biological Safety Cabinet." One additional script on safety in handling laboratory animals was edited. These projects were done in collaboration with the Office of Biohazard and Environmental Control, NCI, and a contractor, Dow Chemical, U.S.A. Negotiations were completed for this series of training materials to be reproduced and sold through the National Audiovisual Center of the National Archives. The NCI sponsored course on "Principles of Biohazard and Injury Control in the Biomedical Laboratory" at the University of Minnesota was evaluated for conversion of lectures and visual materials to slide/tape presentations.

Consultation was provided in planning, preparation and production of various manuals, guides, catalogs and other publications and on the planning, organization and delivery of various presentations for briefings, speeches and seminars.

Consultation began on design and creative direction of a series of TV vignettes for training psychiatric nurses in which coordination between the Clinical Center nurse training office and a contractor was required.

Work continued on building a centralized file of original slides. This file provided materials to a number of NIH lecturers. A second group of historic NIH slides was gathered, identified and prepared for submission to the National Library of Medicine's historic collection.

The Visual Communications Project Officer continued to lecture on effective communication techniques to NIH and NIH-related audiences. He also continued to coordinate and edit DRS scientific documents, reports and visual materials. Liaison was maintained with the NIH/OD, other BIDs on reporting and informational matters.

A slide presentation, "The DRS Story," won an award for writing/editing from the Federal Editors Association.

F. DRS Services Index

The brochure, "Services and Facilities of the Division of Research Services," a catalog for users, was coordinated, written, published and distributed throughout the NIH community. Yearly updating is planned.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1973, through June 30, 1974

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Lester Goodman, Chief

I. SUMMARY

Fiscal Year 1974 was highlighted by the maturing and reduction to practice of several major projects initiated and developed in preceding years. The utility and effectiveness of previous analysis and experimentation were demonstrated via the establishment of mathematically derived chemotherapeutic protocols for managing certain cancer cases, and application of pharmacodynamic principles to achieve more optimal hemodialysis of patients suffering from renal failure. Prototype clinical instrumentation systems based on video technology were accepted as practical tools for monitoring cardiac performance and the condition of aortic ball valve prostheses in vivo; non-invasive ultrasonic imaging for measurement of heart muscle dimensions has become relatively routine. Previously developed concepts and equipment for investigating concussion were regularly used to generate and analyze reproducible data from head injury experiments. Formalized inspection and maintenance routines for patient care apparatus in the Clinical Center were implemented. The Scientific Equipment Rental Program expanded markedly and was broadly accepted and used by a substantial portion of the NIH community as a reliable, economic resource.

Investigations with substantial potential for future applications were initiated in several important areas, including the identification and assessment of trace metallic complexes in cancer therapy and environmental contamination, the interaction of implanted polymers with blood and body fluids, fluid mechanical influences on atherosclerotic plaque formation, ionic concomitants of cortical metabolism, faster and more sensitive microcalorimetry, and comprehensive instrumentation for investigating the behavioral effects of anti-epileptic drugs. New concepts and designs for more reliable and economic mechanized apparatus for materials handling and sample processing were formulated, especially in the context of clinical chemistry; refined surgical tools for ophthalmology and neurology were brought to the proof of concept stage.

Demands for consultation and assistance with collaborative and extramural programs exceeded resources available, as did requests from other government agencies for fabrication of unique technical systems based upon BEIB designs and prototypes.

II. BRANCH PROGRAMS

A. Objectives

To provide direct and consultative engineering support to clinical and biomedical research projects, including advice on systems analysis, experimental design, and synthesis of technical expedients.

To design, develop, fabricate, and evaluate special-purpose devices and systems not commercially available.

To maintain and repair scientific laboratory and clinical equipment.

To obtain and disseminate information on developments and improved production methods in the biomedical engineering and instrumentation fields.

B. Current Programs

The primary purpose of the Branch is to provide service and support to the intramural program of the NIH. BEIB activities, therefore, are identified with many of the individual programs that constitute the intramural research effort. The overall Branch program is best described as the coordinated effort of its operating units.

1. Instrument Fabrication

Production, modification, and minor design of medical equipment and instrumentation systems requiring special tools and skills in the electronic, electrical, glass, mechanical, optical, rubber, plastics, welding, and sheet metal categories.

2. Systems Maintenance

Maintenance and repair of biomedical equipment and instrumentation systems and instruction of technicians and scientists in the proper use and operation of especially complex instruments and devices.

3. Supply

Acquisition and disposition of materials, parts, and equipment required for branch operations and maintenance of controlled inventory stocks and records.

4. Engineering and Applied Science -

Chemical, Electrical and Electronic, and Mechanical:

a. Direct and consultative professional services for fundamental and applied projects relevant to biomedical research and health care at the NIH.

b. Research, design, development, and evaluation related to new instrumentation and equipment.

c. Communication between NIH and the scientific community on engineering support to biomedical research and clinical practice.

5. Satellites

These technical support units, composed of selected engineers and technicians with appropriate shop facilities, are located in certain areas where it is beneficial to make typical BEIB support and service immediately available via a controlled degree of decentralization. They are responsive to demands of local programs and operate as integral parts of the resident team but are administratively responsible to the central Branch. Each satellite is especially tailored to meet specific needs of the host institute or division, supplying it with advantages of a proprietary technical group while maintaining the chief benefits of centralized resources.

C. Program Progress and Accomplishments

1. Technical Services

a. Instrument Fabrication Section

Backlogs increased steadily throughout the year, even though the number of requests for service decreased by 18 percent from the previous year. Response acceptable to investigators was maintained by substantial use of overtime. The section completed approximately 3,700 projects valued at \$750,000 compared with 4,500 projects valued at \$966,000 in FY 1973.

b. Systems Maintenance

Curtailment of preventive maintenance routines, because of reductions in staff, restricted services almost completely to meeting emergency requests, reduced the number of tasks performed, and increased the average cost per assignment. Substantial overtime was necessary to complete approximately 8,200 jobs at a cost of \$1,200,000 compared with 9,600 and \$910,000 respectively in FY 1973.

The Scientific Equipment Rental Program expanded substantially over the year; growth is summarized in the following table:

	<u>July 1, 1973</u>	<u>July 1, 1974</u>	<u>Percent Increase</u>
Number of pool equipment items	330	430	30
Prevailing dollar value	\$390,000	\$485,000	24
Number of items on rental	90	210	133
Prevailing utilization rate	26%	49%	88

	<u>FY 1973</u>	<u>FY 1974</u>	<u>Percent Increase</u>
Gross rental revenue	\$ 22,000	\$ 65,000	195
New rental equipment investment	4,200	17,500	320

Limitations on space and personnel have become serious impediments to the effective operation of this program that has become so popular with NIH investigators.

1. Supply Unit

Reduced levels of activities throughout NIH and substantial price increases resulted in a 5 percent decrease in the number of transactions and a 2.5 percent rise in value of goods sold in comparison with FY 1973. Transactions dropped from 22,000 in the previous year to 21,000 and cost of goods sold rose from \$415,000 to \$426,000.

2. Engineering and Applied Sciences

a. Chemical Engineering

Considerable progress was made in applying principles of chemical reaction engineering to problems of drug, metabolite and trace contaminant distribution in the body. Pharmacokinetic modeling has permitted the elucidation of species differences in both metabolized and nonmetabolized substances. It has also enabled operational assessment of the quantitative importance of physiologic processes and biochemical interactions which determine uptake, distribution and elimination. Of primary concern was the assessment of toxic risk to man of drugs and environmental contaminants on the basis of experiments conducted in animals or from simplified in vitro screens.

The invention of a device for slow controlled release of an anticancer drug provided for more complete comprehension of the biological response of tumor and sensitive normal tissue and suggested methods for improved therapy. A cooperative clinical protocol has been established in which patients will receive drugs at mathematically predicted rates to maintain concentrations known to be effective in experimental systems. Pharmacokinetic and pharmacodynamic principles have been usefully applied to achieve more optimal hemodialytic therapy of patients with kidney failure.

Growing interest in metallic elements in biological systems led to improved methods for assay of platinum in tissues and fluids to support pharmacologic studies and assess risk associated with platinum based catalytic converters on automobiles. The role of calcium in right heart failure of rabbits, after receiving the anticancer drug adriamycin, is being examined. It has been suggested that appropriate use of gallium might protect patients from excessive exposure to radioactive tracers.

Fundamental thermodynamic and kinetic studies of important biomaterials have helped clarify the interaction of multicomponent polymer systems with biological environments. Elution of mobile and potentially toxic materials from the polymer and absorption by the polymer of body constituents, such as lipids, have been studied. A new composite ball heart valve was successfully implanted in a calf, and subsequent experiments are planned. Segmented polyurethane, now commercially available, has been applied successfully in several new biomedical prostheses; high order of biocompatibility and ease of fabrication continue to offer further exciting prospects for biomedicine.

The roles of fluid mechanics, transport and kinetics are being examined in the development and progression of atherosclerosis. An electrochemical technique was developed to study shear stress distributions in a model of the canine aorta near bifurcations where plaque formation arises. The experimental investigation is being supported by hydrodynamic analyses.

Extensive consultation was provided to a variety of intramural, collaborative, and extramural programs.

b. Electrical and Electronic Engineering

BEIB completed a substantial number of new designs for electrical and electronic apparatus for the NIH research program; projects deserving special mention are summarized as follows:

New developments in clinical instrumentation include a noninvasive televised technique for detecting artificial aortic valve ball variance; a dual ion-selective microelectrode and associated electronics for measuring K^+ ion concentration in cortex; a low dose level, high resolution dental X-ray system; advances in dynamic two-dimensional organ visualization via ultrasonic scanning; and a special purpose audio stimulator for assessing behavioral side effects of anti-epileptic drugs.

Noteworthy laboratory instrumentation projects produced a rapid biological cell freezing system; faster, more accurate measurement and signal processing apparatus for microcalorimetry; enhancement of the ^{13}C NMR system performance; a nuclear isotope raster scan and mapping process; and a novel frequency domain fluorescence decay analyzer.

The patient electrical safety program featured inauguration of formalized inspection and maintenance routines for much of the critical patient care apparatus in the Clinical Center, utilizing previously developed and new automatic test equipment.

EEES provided substantial support to the NHLI/NASA team, evaluating the effects of prolonged weightlessness on Skylab astronauts, and extensive consultation to numerous other intramural, collaborative and extramural programs.

c. Mechanical Engineering

Continued close collaboration with research and service staff throughout the NIH resulted in several substantial developments. Mechanization and automation of routine procedures received emphasis. Efficiency and effectiveness of biological sample analyses were enhanced via several new automatic materials handling devices for aliquots and reagents. Distinct improvements were achieved in methods for large-scale processing of laboratory glassware and media. These systems continue to reduce the cost and time of routine manual tasks and enable reallocation of manpower to more productive and challenging assignments.

Considerable attention was devoted to fundamental and applied research on the mechanisms of head injury, processing of electrophoretic preparations,

physiological effects produced by mechanical stress on nerve tissue, mechanisms of eye lubrication, and effects produced on unborn infants by elevated temperature in the mother.

The state of the art in recording electrical signals from the brain, in vivo, was advanced with the innovation of devices for precise atraumatic insertion of electrodes into cortical regions; and for remote eye surgery using a chin-operated "joy stick" which manipulates all adjustments on a microscope during operations, thus freeing the hands of the surgeon for other functions.

Extensive consultation was provided to intramural, collaborative, and extramural programs.

d. Florence Agreement

Fulfilling the NIH responsibility related to the "Florence Agreement" has been delegated to BEIB. Duties involve review of applications for duty-free entry of foreign manufactured scientific apparatus acquired by domestic nonprofit institutions, assessment of the suitability of equipment cited for the intended application, investigation of availability of domestically produced scientific equivalents, recommendations to the U. S. Department of Commerce for approval, disapproval, or resubmission; and providing pertinent technical advice to requesting agencies and the Department of Commerce. Activities for FY 1974 are summarized as:

Number of applications received by NIH.	580
Referred to other agencies.	90
Processed by NIH.	490
Processed independently by NIH Florence Agreement	
Committee Executive Secretary (BEIB).	420
Processed with help of other Committee members.	70
Recommendations for approval.	350
Recommendations for disapproval.	10
Recommendations for resubmission.	130

The Executive Secretary, as a result of the need to be thoroughly knowledgeable in modern scientific equipment, has become recognized as a reliable source of expert guidance, especially in the areas of transmission and scanning electron microscopy.

3. Technical Advances

A NOVEL DENTAL DIAGNOSTIC SYSTEM incorporating X ray, electrooptical data acquisition, image enhancement, and video processing provides improved displays with sharply reduced radiation exposure.

A PLASTIC PHANTOM HEAD MODEL is useful in assessing the spatial and absorptive resolution of transverse axial tomography systems.

A THIN FILM CAPACITIVE SENSOR in a resonant bridge and lock-in amplifier substantially enhances speed and resolution of temperature measurements.

A NONDESTRUCTIVE BONE STRENGTH TESTER enables examination of periosteum and oxygen effects on the healing rate of fractures.

AN AUDIO STIMULATOR, lightweight and battery powered, features flexibility in generating programmed clicks and white noise for right and left ears and provides reference signals for computer processing.

CHOLESTEROL DEPOSITS ON ARTERY WALLS are automatically mapped on excised, expanded sections using a digitally driven Geiger tube, in a raster mode, to detect radio tracer intensity.

AN OSCILLATING PRIMATE TURNTABLE, under servo control, enables frequency response studies of central vestibular units being stimulated by rotation of the semicircular canals.

AN IMPROVED SYNCHRONOUS GATE used with the superconducting FFT NMR system reduces test time by an order of magnitude by enhancing the nuclear Overhauser effect without disturbing the ^{13}C fine structure arising from proton couplings.

PREDETERMINED CORTICAL CONTUSIONS and intracranial pressure transients for studying head injury phenomena in primates are generated by a high performance servo controlled drive system.

A HYPOTHERMIA CHAMBER elevates temperature in pregnant sheep to enable investigation of the effect of fever on the fetus.

POTASSIUM ION CONCENTRATION in exposed cat cortex, measured with ion selective electrodes, together with ECG and NADH monitoring helps clarify the relationship between neural activity and potassium ion transport.

A FLUORESCENCE DECAY RATE MEASUREMENT SYSTEM for dynamic studies of stimulated squid axon, permitting illumination at 10^7 times greater than commercial apparatus markedly enhances speed and sensitivity of detection.

A SWITCHED GAIN ULTRASONIC SCANNER substantially improves the clarity and accuracy of cardiac structure images.

A VITREOUS HUMOR EXCHANGE DEVICE facilitates eye surgery by enabling one-handed control of intraocular fluid volume by the surgeon.

AN INFANT BEHAVIOR MONITOR generates visual and aural stimuli while recording movement responses to help elucidate the phenomena of mother-child interaction.

AN ISOLATED ORGAN PERFUSION CHAMBER maintains viability and enables prolonged study of excised animal hearts and kidneys for research on transplantation.

A CLINICAL FLOW MICROCALORIMETER provides for rapid thermochemical analysis of patient blood.

AN IMPROVED PHOTOELECTROSPECTROPHOTOMETER extends ability to analyze molecular structures with ultraviolet radiation.

A LYMPHOCYTE HARVESTER mechanizes the transfer of cell samples from microtiter tray wells to filter paper for subsequent processing.

PORTABLE ANIMAL ISOLATORS incorporating self-contained air handling expedite transportation and holding of small animals.

OPTIMUM COOLING OF BIOLOGICAL MATERIALS through liquid, eutectic, and solid phases is enabled by a novel feedback temperature control system.

4. Training

An effective professional and technical training program was essential in maintaining high quality support and service to the NIH programs. Forty-five employees participated in 67 academic, administrative and technical courses. Six (65 man-days) undertook formal university education and training courses. Eight (37 man-days) received specialized training on scientific equipment at manufacturers' facilities and at the NIH. Thirty-one attended various administrative, clerical, technical and scientific courses and training seminars. One employee attended Basic Adult Education at NIH sponsored by the Montgomery County School System and five were enrolled in the Upward Mobility College.

The Glassblower Trainee, hired under the Affirmative Action Program and subsequently promoted to the WG-8, Intermediate level, was promoted in FY 74 to Glassblower, WG-10, after demonstrating proficiency at the higher grade. A second Glassblower Trainee was hired, bringing to four the total number of employees at various stages of development under this program. All are continuing to receive academic instruction at local colleges and technical schools, as well as intensive on-the-job training.

D. Program Plans

Fiscal 1974 was distinguished by the reduction to practice and practical demonstration of several important concepts and designs innovated in preceding periods.

1. Considerable attention will be devoted in the coming year to refining, reinforcing, and extending applications in the laboratories and clinics, especially in the areas of:

- a. Mathematical prediction and implementation of optimized chemotherapy and dialysis.
- b. Noninvasive physiological measurements.
- c. Rational design of long-term implanted prostheses.
- d. Mechanized and automated materials handling.
- e. Elucidation of electrical, mechanical, and chemical concomitants of neural, muscular, and cardiovascular phenomena.
- f. Standardized hospital safety functional and operational criteria.

2. Allocation of additional space for the Scientific Equipment Rental Program is expected to alleviate a serious constraint and enable more effective operation and service to the NIH community.

3. Utilization of available opportunities to supplement BEIB staff and indoctrinate career aspirants is contemplated; substantial use of programs such as Intergovernmental Personnel Act (IPA), Project Access, Project Stride, Excepted "Schedule A" appointments for students and faculty members, Stay-in-School, and EEO Affirmative Action Plan Training is anticipated.

4. Efforts will be made to increase collaborative intradivision activities to improve the quality and timeliness of DRS support for the entire NIH.

5. The effectiveness with which BEIB implements these plans and fulfills its mission depends crucially on the availability of adequate staff. Prevailing constraints must be relaxed if satisfactory performance is to be provided.

E. Publications and Patents

1. Publications

Bischoff, K.B.: Commentary on pharmacokinetics. In Iberall, A.S. and Guyton, A.C. (Eds.): Regulation and Control in Physiological Systems. Proceedings of the Conference, August 22-24, 1973, University of Rochester, Rochester, N.Y. Pittsburgh, Instrument Society of America, 1973, pp. 54-56.

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2. Patents

No report.

III. INDIVIDUAL PROJECT REPORTS

Serial No. DRS-BEIB-1

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Pharmacokinetics

Previous Serial Number: Same.

Principal Investigators: Robert L. Dedrick, Daniel S. Zaharko

Other Investigators: Henry L. Gabelnick, Richard A. Bender,
Anthony M. Guarino, Robert J. Lutz,
Kenneth B. Bischoff

Cooperating Units: LCHPH-NCI, LT-NCI, OD-NIEHS, AK-CU Program NIAMDD

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants and endogenous metabolites in animals and man to:

- (1) Account for species differences in drug distribution.
- (2) Provide rational bases for extrapolation of toxicity from animals to man.
- (3) In conjunction with pharmacodynamics, provide a basis for optimization of cancer chemotherapy and chronic hemodialysis.
- (4) Enable rational transfer of in vitro metabolic data to in vivo cases.
- (5) Predict effective dose schedules of anti-cancer drugs in individual patients.

Methods Employed: Mathematical models are developed from physicochemical, physiological and anatomical information and the principles of chemical reaction engineering. Resulting differential equations sets are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

- (1) Pharmacodynamics of methotrexate have been further clarified by extensive studies with constant infusion in mice from a new implantable device.
- (2) Methotrexate uptake by canine lymphosarcoma appears to be described by a modified form of a model developed for normal rat tissues.
- (3) A pharmacokinetic model, originally developed on the basis of extensive studies in mice, is adaptable to predict plasma concentrations in individual patients.
- (4) During chronic hemodialysis:
 - (a) Significant intercompartment transport resistance may cause chemical disequilibrium.
 - (b) Patient response may be significantly delayed after a change in treatment.
 - (c) Patient response may be more dependent on dialysis schedule than generally realized.

Significance: Drugs and other chemicals are tested for effect in animals, and the extrapolation to man is a subject of serious concern. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued emphasis on pharmacokinetic modeling with particular attention to pharmacodynamic and cytokinetic events. Increased emphasis on clinical applicability through prediction of most effective individual patient dose schedules.

Honors and Awards: None.

Publications:

Bischoff, K.B.: Commentary on pharmacokinetics. In Iberall, A.S. and Guyton, A.C. (Eds.): Regulation and Control in Physiological Systems, Proceedings of the Conference, August 22-24, 1973, University of Rochester, Rochester, N.Y. Pittsburgh, Instrument Society of America, 1973, pp. 54-56.

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Himmelstein, K.J. and Bischoff, K.B.: Mathematical representations of cancer chemotherapy effects. J. Pharmacokinet. Biopharm. 1: 51-68, 1973.

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Straw, J.A., Hart, M.M., Klubes, P., Zaharko, D.S., and Dedrick, R.L.: Distribution of anticancer agents in spontaneous animal tumors. 1. Regional blood flow and methotrexate distribution in canine lymphosarcoma. J. Natl. Cancer Inst. (In press)

Teorell, T., Dedrick, R.L., and Condliffe, P. (Eds.): Pharmacology and Pharmacokinetics. (In press)

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_____ and _____: Pharmacokinetic models: Application to antineoplastic agents. In Sartorelli, A.C. and Johns, D.G. (Eds.): Handbook of Experimental Pharmacology, Antineoplastic and Immunosuppressive Agents I. (In press)

_____, _____, and Oliverio, V.T.: Prediction of the distribution of methotrexate in the sting rays dasyatidae sabina and sayi by use of a model developed in mice. Comp. Biochem. Physiol. 42A: 183-194, 1972.

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Serial No. DRS-BEIB-2

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Trace Element Analysis in Biological Materials (new title)

Previous Serial Number: Same.

Principal Investigators: André F. LeRoy, Harry M. Olson, Anthony M. Guarino

Other Investigators: Robert L. Dedrick, Charles L. Litterest,
Theodore E. Gram, Rebecca E. Munroe,
Harry L. Sponseller

Cooperating Unit: LT-NCI

Man Years:

Total:	2.0
Professional:	1.2
Other:	0.3

Project Description:

Objectives: Improve analysis and identification of metal complexes in biological materials. Enhance analytical methods with detection limits in the order of nanograms to picograms in one milligram samples, with emphasis on analysis of Pt and Ga compounds used in cancer therapy. Platinum group metals will become environmental trace contaminants if catalytic exhaust systems are used to control emissions. Emphasis also on analysis of Ca and Mg in tissue that appear to interact with an antineoplastic drug, Adriamycin, with frequent right heart failure of humans and test animals.

Methods Employed: Flameless atomic absorption spectrophotometry to analyze for specific elements. Successful direct analysis of biological tissue by this means has been limited; procedures with chemical agents are used to promote release of metals from the biological matrix with smoother, more complete combustion. Cleaner combustion can be realized in some cases with solvent extraction.

Electrophoresis to separate protein fractions and determine distribution of metal species among fractions. Biopsy drills may be used to obtain cardiac muscle samples for calcium and magnesium analysis.

Major Findings: Sensitivity of platinum determination is presently about one nanogram. Urine samples from monkeys treated with cis-dichlorodiammine platinum were analysed by methods described. Determinations on liquid and precipitated solids showed 40-100 times more in liquid than in solids in 64 samples collected from 10 monkeys. Sensitivities for Ca and Mg are approximately 40 and 3 picograms respectively, using the flameless atomic absorption spectrophotometer. The best sensitivities are realized with samples pretreated by dry or wet ashing.

Significance: Quantitation and identification of metals at trace levels in biological tissue is important for cancer therapy. Characterization of such compounds and assays in tissues and body fluids can help identify drug action and suggest other potentially useful compounds. These methods offer an alternative to administering radio labelled substances to human subjects.

Analysis of trace contaminants is necessary in establishing priorities for environmental control.

Proposed Course: Broaden applicability of direct combustion method to more tissue types. Modify electronic temperature programmer and use feedback control to regulate rate of temperature increase. Determine detailed time course of drug concentration in blood and urine samples after single doses and correlate with pharmacokinetic models for better understanding of drug behavior. Pursue Ca and Mg tissue analysis in more detail; e.g., in cardiac mitochondria to better define site of drug-metal interaction.

Honors and Awards: None.

Publication:

LeRoy, A.F. and Morris, J.C.: The kinetics of hydrolysis of rutheniumnitrosyltrichloride. J. Inorg. Nucl. Chem. 33: 3437-3453, 1971.

Serial No. DRS-BEIB-3

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis

Previous Serial Number: Same.

Principal Investigators: Robert J. Lutz, Joseph N. Cannon

Other Investigators: Donald L. Fry, Robert L. Dedrick, Kenneth B. Bischoff, Robert K. Stiles

Cooperating Units: OD-IR-NHLI, Howard University

Man Years:

Total:	1.0
Professional:	1.0
Other:	.0

Project Description:

Objectives: Measure shear stress on the inner wall of simulated arteries during steady and pulsatile flow and correlate data with localization of atherosclerosis as found in experimental animals.

Methods Employed: An electrochemical technique is used, based on an oxidation-reduction reaction at electrodes implanted at a fluid-solid interface, which determines mass transfer rates of redox ions. Velocity gradients at the wall (shear rate) are calculated from mass transfer rates with suitable boundary layer equations.

Major Findings: Shear stress experiments in rigid casts of the canine arterial tree indicate peaks in shear stress near bifurcation points and branches, which are also regions of high plaque involvement in experimental animals. Pulsatile flow generated disturbances between branches and produced mean shear stresses higher than steady shear stresses at the same average flow rate. A pseudo-steady state approximation to the mass transfer boundary layer equations is adequate for calculating time varying shear stresses during low frequency sinusoidal flow.

Significance: Elucidation of the role of hemodynamics and mass transfer in the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease.

Proposed Course: Extend experimental studies to steady and pulsatile flow in distensible arterial models. Investigate the role of other (salient) transport properties of the arterial wall in models of arteries; e.g., ultra-filtration of large molecular weight lipoproteins, and diffusion through medial sections of arterial wall.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-4

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Implant Device Development

Previous Serial Number: None.

Principal Investigator: John W. Boretos

Other Investigators: John W. Brown, William S. Pierce, Robert E. Baier,
Robert D. Stiehler, André F. LeRoy, Robert L. Dedrick

Cooperating Units: SB-NHLI, National Bureau of Standards,
Pennsylvania State University, Calspan Corporation

Man Years:

Total:	1.5
Professional:	1.2
Other:	0.3

Project Description:

Objectives: Elucidate the interaction of polymers used for specific implants with the physiological environment; explore specially prepared polymers and design features.

Methods Employed: Basic polymer composition is carefully controlled and modification of cross-linking systems is employed. Rheological properties are studied as a function of cross-linking. Implants are examined after removal for lipid absorption, protein deposition, changes in surface free energy, and alteration of physical properties. Observations include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis and atomic adsorption spectroscopy.

Major Findings: Ten heart assist devices with segmented polyurethane blood contact surfaces were implanted in calves for up to 35 weeks. No lipid absorption was observed; physical strength remained stable; surfaces developed a biocompatible protein layer.

A series of ventricular-aortic bypass devices functioned satisfactorily for periods up to 17 weeks in dogs with minimal blood damage. This procedure may be suitable for future clinical use.

Cure schedules for silicone rubber appear to affect failure of heart valve poppets.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart assist devices and vascular implants. Characterization of blood-material interaction is essential to successful performance and must be established before clinical use can be justified.

Proposed Course:

- (1) Extend experimental studies to further characterize the surfaces and bulk properties of segmented polyurethane to determine more specific information on its blood interaction.
- (2) Study the cure systems of silicone rubber to reduce inherent stresses and inadequately combined chemical portions.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-5

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Multicomponent Plastics in Biomedical Use

Previous Serial Number: Same.

Principal Investigator: Henry L. Gabelnick

Other Investigator: Margaret L. Wehling

Cooperating Units: None.

Man Years:

Total:	0.6
Professional:	0.4
Other:	0.2

Project Description:

Objectives: Extend definition of the interaction of plastic systems with the biological environment, emphasizing the kinetics of additive elution from polymers and absorption of body constituents.

Methods Employed: Determination of concentration vs. time profiles of migrating species via quantitative analytical techniques. Parameters under investigation include fluid composition and flow conditions.

Major Findings: Refined analytical techniques enable evaluation of the di-2-ethylhexylphthalate-polyvinyl chloride system exposed to a soybean emulsion "pseudo-serum." Preliminary runs on a simulated artificial kidney show promise.

Significance: Physiologically compatible, stable materials with desirable physical properties are needed for many biomedical applications. Characterization of desorption rates for additives from polymer systems and absorption of bodily constituents are important in determining the utility of implant materials.

Proposed Course:

- (1) Refinement of analytical techniques.
- (2) Kinetic studies in flow systems to define the rate-limiting steps.
- (3) Absorption studies including effects on physical properties.

Honors and Awards: None.

Publications:

Boretos, J.W. and Gabelnick, H.L.: Letters to the Editor. Characterization of biomedical polymers. J. Biomed. Mater. Res. 7: 267, 1973.

Gabelnick, H.L.: Biorheology. In Lapedes, D.N. (Ed. in Chief): McGraw Hill Yearbook of Science and Technology. New York, McGraw Hill, 1973, pp. 66-74.

_____ and Litt, M. (Eds.): Rheology of Biological Systems. Springfield, Ill., Charles C Thomas, 1973, 319 pp.

Serial No. DRS-BEIB-6

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Nuclear Magnetic Resonance Techniques for Biochemical Analysis

Previous Serial Number: Same.

Principal Investigators: Thomas R. Clem, Walter S. Friauf, Edwin D. Becker

Other Investigator: James A. Ferretti

Cooperating Units: LCP-NIAMDD, PSL-DCRT

Man Years:

Total:	4.0
Professional:	3.0
Other:	1.0

Project Description:

Objectives: Innovate and implement improved methods for structural elucidation of organic molecules by means of nuclear magnetic resonance with emphasis on ^{13}C .

Methods Employed: Develop and evaluate techniques for improving sensitivity and versatility, including use of a superconducting magnet, pulse train excitation with digital programming of the sequences, heteronuclear decoupling, real time computerized data acquisition, digital averaging, phase correction, matched filtering, Fourier transformation, and printout of spectra.

Major Findings: NMR technique can be successfully extended to the characterization of nuclei other than ^{13}C , including ^{23}Na and ^{79}Br .

Significance: The system now approaching the status of a routine laboratory instrument, offers unprecedented capability for elucidation of organic molecule structure and, in particular, the location of ^{13}C , et al., atoms. The high field strength of the superconducting magnet enables finer resolution than is obtainable with most other ^{13}C NMR apparatus.

Proposed Course: Modifications with a second superconducting magnet to enable experiments with full-time application to ^{13}C and related atoms; to extend capability to other nuclei, such as ^{27}Al , ^{14}N , ^{15}N , and ^{55}Mn .

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-7

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973, through June 30, 1974

Project Title: Television Image Processing Techniques for Biomedical Research

Previous Serial Number: Same.

Principal Investigator: William H. Schuette

Other Investigators: James A. Dvorak, Leonard E. Grauer, Darrell V. Lewis,
David R. Redwood, John M. Van Buren, Richard L. Webber,
Willard C. Whitehouse

Cooperating Units: LPD-NIAID, CB-IR-NHLI, EEG-NINDS, SN-NINDS, OMS-NIDR,
ADM-CC

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Objectives: Develop and apply new and improved techniques for analyzing television signals in the context of medical research. Enhance effectiveness of television based systems for the collection and processing of biomedical data.

Methods Employed:

(1) A semiautomatic method calculates left ventricular volumes directly from televised fluoroscopy; ventricular silhouette tracings are electronically analyzed and volumes determined utilizing realistic geometrical assumptions.

(2) A logarithmic television densitometer obtains the left ventricular net forward ejection fraction; the exponential decay rate of the washout curve following an LV X-ray dye injection is utilized to calculate the ejection fraction.

(3) Television based apparatus analyzes changes in fluorescence occurring in exposed cortex during neurosurgery; fluorescence changes, related to metabolism over large areas and the activity from several regions are compared simultaneously.

- (4) A quantum limited dental X-ray prototype has been successfully tested.
- (5) A video system measures and digitally displays cell areas and volumes from image traces.
- (6) A technique for inserting analog data into the television format correlates auxiliary information with video signals.

Major Findings: Image amplifiers enable low light level applications previously reserved for photomultiplier tubes. The methods of (1) and (2) above, now in routine use in the catheterization laboratory, show excellent correlations, $r = 0.98$, in patients with normal ventricles. Analysis of televised fluorescence in conjunction with extracellular potassium ion concentrations reveals novel relationships between the kinetics of ion transport and metabolism. Video signals obtained for other purposes often produce valuable new quantitative data. Semiautomatic processing with analog circuitry and human involvement, at the proper level, can be more cost effective than fully automated computer processing.

Significance: These developments extend noninvasive testing and provide increased quantitative data for research and make treatment feasible which would otherwise be impractical. The televised fluorometer has launched new investigations on the metabolism of exposed human cortex.

Proposed Course: Continue to work in established directions to improve available systems.

Honors and Awards: None.

Publications:

Dvorak, J.A., Schuette, W.H., and Whitehouse, W.C.: A simple video method for the quantifying of geometric parameters of microscopic objects. J. Microsc. (In press)

Levitsky, S., Schuette, W.H., Kempner, K.M., Sloane, R., Souther, S.G., Mullin, E.M., and Morrow, A.G.: Experimental and early clinical evaluation of heart tracking (Radarkymography) as a noninvasive method for measuring myocardial contractility. Am. J. Cardiol. 32: 156-161, 1973.

Lewis, D.C., O'Connor, M.L., and Schuette, W.H.: Oxidative metabolism during recurrent seizures in the penicillin treated hippocampus. Electroencephalogr. and Clin. Neurophysiol. (In press)

Marcus, M.L., Schuette, W.H., Whitehouse, W.C., Bailey, J.J., Douglas, M.A., and Glancy, D.L.: Use of a video system in the study of ventricular function in man. Am. J. Cardiol. 32: 175-179, 1973.

_____, _____, _____, _____, and Glancy, D.L.: An automated method for the measurement of ventricular volume. Circulation, XLV: 65-76, 1972.

Schuette, W.H.: Video-log: A technique for recording analog signals in the television video format. Proceedings of the Eleventh Annual Rocky Mountain Bioengineering Symposium and Eleventh International ISA Biomedical Sciences Instrumentation Symposium, USAFA. (In press)

Thompson, E.J., Wilson, S.H., Schuette, W.H., Whitehouse, W.C., and Nirenberg, M.W.: Measurement of the rate and velocity of movement by single heart cells in culture. Am. J. Cardiol. 32: 162-166, 1973.

Serial No. DRS-BFIB-8

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973, through June 30, 1974

Project Title: Diagnostic Ultrasound

Previous Serial Number: Same.

Principal Investigator: James M. Griffith

Other Investigators: Walter L. Henry, William R. Brody, P. David Myerowitz,
Barry J. Maron, Stephen E. Epstein, Robert E. Goldstein

Cooperating Units: CB-IR-NHLI, SU-IR-NHLI

Man Years:

Total:	3.0
Professional:	1.5
Other:	1.5

Project Description:

Objectives: Noninvasively obtain dynamic measurements of cardiac geometry and function to quantitate wall thickness, transverse ventricular dimensions, and valve motions; to directly measure blood flow.

Methods Employed: A gain switching technique was developed to increase the dynamic range of recorded information in one- and two-dimensional scans.

Two probes were developed for use in dogs: (1) a pulse-echo probe, sutured directly to the heart wall, measures wall thickness and chamber size for clinical studies; (2) a cw doppler probe measures aortic flow.

A real time two-dimensional sector scanner, previously reported, was improved to provide faster scan rates and wider view angles.

Major Findings: Work completed during the past year has further enlarged the amount of quantitative data obtainable from routine ultrasound studies. For example, the diagnosis of congenital heart malformations is very encouraging.

Significance: Safe noninvasive methods for making quantitative measurements of cardiac dynamics is of substantial value for diagnostic and research purposes.

Proposed Course: Refine and further develop present systems. It is believed that a number of significant techniques will yet develop; for instance, a range-gated doppler flowmeter optimized for cardiac geometry.

Honors and Awards: None.

Publications:

Griffith, J.M. and Henry, W.L.: A real time system for two-dimensional echocardiography. In Proceedings of the 26th Annual Conference on Engineering in Medicine and Biology, 1973, Minneapolis, Minnesota. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1973, Vol. 15, p. 422.

_____ and _____: Video scanner-analog computer system for semiautomatic analysis of routine echocardiograms. Am. J. Cardiol. 32: 961-964, 1973.

Serial No. DRS-BEIB-9

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Measurement of Low Level, Rapid Chemical Reaction Rates by Laser Jump, Temperature Jump and Stopped Flow Techniques

Previous Serial Number: Same.

Principal Investigators: Michael Greifner, P. Boon Chock

Other Investigators: None.

Cooperating Unit: LB-IR-NHLI

Man Years:

Total:	1.0
Professional:	0.75
Other:	0.25

Project Description:

Objectives: Measure incremental parameter changes corresponding to important biochemical reactions over a wide dynamic range. Develop a system capable of detecting and displaying chemical reaction rise times of less than 100 nanoseconds.

Methods Employed: Light absorption and fluorescence are monitored with photo-multipliers. Dynode switching provides wide dynamic range without impairment of frequency response, linearity or accuracy. High intensity pulsed light sources improve the signal to noise ratio of nanosecond absorption measurements. Signal averaging techniques recover low level signals otherwise obliterated by noise.

Major Findings: Stopped flowmeters with increased sensitivity provide an order of magnitude improvement in absorption level detections over commercially available instruments. Higher sensitivity is required to detect especially low level enzyme reactions.

Significance: Improved system sensitivity and frequency response enable new exploratory investigations into the complex mechanisms of various enzyme functions. State of the art instrumentation for temperature jump apparatus and stopped flowmeters can provide information on the incremental, fast interactions between antibiotics with enzymes or proteins.

Proposed Course: Complete evaluation of stopped flowmeter reaction times. Test and evaluate temperature jump apparatus. Initiate investigation into laser jump technique feasibility.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-10

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973, through June 30, 1974

Project Title: Automatic Test Set for Evaluating Electrical Safety of Clinical Equipment

Previous Serial Number: Same.

Principal Investigators: Walter S. Friauf, Horace E. Cascio

Other Investigators: Roland Corsey, Anthony J. Vita

Cooperating Unit: ADM-CC

Man Years:

Total:	1.5
Professional:	0.5
Other:	1.0

Project Description:

Objectives: Improve performance and economy of routine electrical safety testing programs for hospital equipment and enhance the accuracy, reliability and safety of medical apparatus.

Methods Employed: Design, construction, testing, and evaluation of an automated test system that satisfies published criteria on electrical safety standards.

Major Findings: Performance of the prototype test set has proven satisfactory, and formalized scheduled inspection routines have been inaugurated. A second generation unit featuring several refinements has been designed and built.

Significance: Hospital electrical safety requires a great many routine tests at relatively short intervals which can be performed only with the aid of automatic test equipment. This is particularly true in a clinical research environment where a great variety of equipment is encountered and inconvenience to patients and medical staff must be minimized.

Proposed Course:

- (1) Evaluate second generation unit.
- (2) Perform trend analysis on test data.
- (3) Disseminate information on the unit to other facilities and to potential manufacturers.

Honors and Awards: None.

Publication:

Friauf, W.S., Cascio, H.E., and Jones, A.R.: Automated test set for checking biomedical equipment. Med. Electron. Data 4: 54-60, 1973.

Serial No. DRS-BEIB-11

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Biomechanical Concomitants of Head Injury/Head Injury Model Program

Previous Serial Number: Same.

Principal Investigators: Ayub K. Ommaya, Lawrence E. Thibault

Other Investigators: None.

Cooperating Units: SNB-NINDS, BEIB-DRS, Department of Transportation, Armed Forces Radiobiology Research Institute

Man Years:

Total:	2.5
Professional:	2.0
Other:	0.5

Project Description:

Objectives: With animal and physical models attempt to validate finite element analytical efforts. Extend the physiological studies previously reported to larger primates with specific reference to the somato-sensory evoked response.

Methods Employed: Experimental and analytic techniques guided by the state of the art in biomechanics. Computer analysis of electrophysiology changes related to mechanical trauma. Mechanical load measurement using implantable neutral density (with respect to brain tissue) transducers.

Major Findings: The somato-sensory evoked response can be modulated by controlled inertial loading of the head. When rotational components of angular acceleration are minimized, analytical models predict reduced shearing strains and evoked responses show minimum changes.

Significance: The evoked response technique should prove to be a significant clinical tool for diagnosis and management of head injuries. Correlations between changes in electrophysiologic parameters and mechanical loads should help establish national criteria for determining injury thresholds.

Proposed Course: Extend the physiological studies in order to gain insight into the sequellae of controlled forms of injury. Continue the analytical model validation effort.

Honors and Awards: None.

Publications:

Gennarelli, T.A., Ommaya, A.K., and Thibault, L.E.: Comparison of translational and rotational head motions in experimental cerebral concussion. In Proceedings of Fifteenth Stapp Car Crash Conference, November 17-19, 1971. Coronado, California. New York, Society of Automotive Engineers, Inc., 1972, pp. 797-803.

_____, Thibault, L.E., and Ommaya, A.K.: Pathophysiologic responses to rotational and translational accelerations of the head. In Proceedings of Sixteenth Stapp Car Crash Conference, November 8-10, 1972, Detroit, Michigan. New York, Society of Automotive Engineers, Inc., Lawrence M. Patrick, Chairman, pp. 296-308.

Ommaya, A.K., Gennarelli, T.A., and Thibault, L.E.: Traumatic unconsciousness: Mechanics of injury to the brain in violent shaking of the head. In Proceedings of the American Association of Neurological Surgeons, 1973. (In press)

Serial No. DRS-BEIB-12

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report
July 1, 1973, through June 30, 1974

Project Title: Atraumatic Electrical Sensing in Human Brain Cortex

Previous Serial Number: Same.

Principal Investigator: Seth R. Goldstein

Other Investigator: Edward M. Schmidt

Cooperating Unit: LNLC-NINDS

Man Years:

Total:	1.6
Professional:	1.0
Other:	0.6

Project Description:

Objectives: Achieve stable electrode location with respect to an active neuron for reliable acute recording of brain cell activity within the pulsating cortex at prescribed depths up to 0.5 cm with minimum tissue damage.

Methods Employed: A conducting wire electrode is held within a gas bearing in the pulsating cortex at the desired insertion angle. A fine lead screw is actuated by gas thrust bearings to retain the "floating" action during electrode depth adjustment.

Major Findings: The device has been successfully tested on a monkey; high quality recordings of neuroelectric potentials for prolonged durations have been produced.

Significance: Single cell electrical recording from cerebral cortex in humans has been limited because of difficulty in atraumatically eliminating the effects of cortical motion. This new method is expected to markedly improve the acquisition of valid information necessary to enhance understanding of brain function.

Proposed Course: Testing and evaluation with animals and humans, refinement of techniques and apparatus, if necessary; clinical applications; enlargement of device family for related types of measurement requirements.

Honors and Awards: None.

Publications:

Goldstein, S.R.: Atraumatic recording from exposed pulsating human cortex--a new mechanism. In Proceedings of the 25th Annual Conference on Engineering in Medicine and Biology 1972, Bal Harbour, Florida, vol. 14. Arlington, Va., The Alliance for Engineering in Medicine and Biology, Samuel P. Asper, M.D., Chairman, p. 190.

_____ and Saleman, M.: Mechanical factors in the design of chronic recording intracortical microelectrodes. IEEE Trans. BME. BME-20, 260-269, 1973.

Serial No. DRS-BEIB-13

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973, through June 30, 1974

Project Title: Pregnant Sheep Hyperthermia: Effect of Elevated Body Temperature on Fetal Vitality

Previous Serial Number: None.

Principal Investigators: Gary K. Oaks, Howard D. Metz

Other Investigators: Ronald A. Chez, Michael Epstein, Alan R. Fleischman, Robert Sefalo

Cooperating Units: PRB-NICHHD, National Naval Medical Center

Man Years:

Total:	1.5
Professional:	1.0
Other:	0.5

Project Description:

Objectives: Determine the effects of hyperthermia on the fetus by examining changes in umbilical blood flow, blood gas concentrations, and other vital processes.

Methods Employed: Induce hyperthermia in pregnant sheep and measured blood gases, umbilical and uterine blood flow. The animal's body temperature is raised by modifying its environment to curtail transfer of endogeneous heat.

Major Findings: Reproducible hyperthermia levels can be consistently produced by constraining the ability of the animal to control the elimination of metabolically generated heat. The environmental chamber designed for these studies has been tested and will be put into routine use.

Significance: Elucidation of fetal disorders due to excessive mother body temperature in animals, upon extension to humans, can lead to improved prenatal and perinatal diagnoses and treatment.

Proposed Course: Complete experimental protocols with sheep and extend to human cases.

Honors and Awards: None.

Publications: None.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1973 through June 30, 1974

ENVIRONMENTAL SERVICES BRANCH

Vinson R. Oviatt, Chief

I. SUMMARY

The Environmental Services Branch devoted major program effort to assessment of chemical carcinogen hazards; procurement of laminar flow biological safety cabinets; and review of laboratory facilities working with potentially hazardous Class III, IV and "non-natural" organisms. All of these were in direct assistance to the intramural research programs and carried out in cooperation with other NIH program elements. Most notable review of laboratory facilities was in association with the NIAID for compliance with the "Memorandum of Understanding and Agreement" for the safe handling of Adenovirus Type 2 - SV40 Hybrids.

A survey of chemical carcinogen usage was initiated in response to tentative standards under the Occupational Safety and Health Act. Preliminary data provided basic information on chemical carcinogen use in research environments to the DHEW panel of experts formulated to develop standards. The NIH response was the most comprehensive of any developed within DHEW. At NIH there are approximately 150 users of chemical carcinogens, 63 whom reported using one or more of the 14 designated chemical carcinogens of interest to the Department of Labor. An NIH program is now being formulated to deal with proper carcinogenic chemical identification, risk assessment, and control measures to be employed. Employee education will be included as a control measure.

Procurement of laminar flow biological safety cabinets at NIH reached a crisis point during the year because of unexpected demand for this safety device--not only at NIH where it was developed, but in outside laboratories. Seventy-five new LFBSC's were put in use with approximately 100 more on order at the end of the fiscal year. The NIH specification for the cabinets was modified three times during the year. These covered dimensional tolerances, human engineering factors, velocity standards, and test procedures. The office of Materiel Management was informed by GSA late in the year that NIH could proceed with the development of a Qualified Products List for this equipment. The first LFBSC's constructed to NIH specifications were purchased during the year.

Major decontamination projects were those of the facilities at the Patuxent research facility vacated by NINDS and animal rooms in Building 37 for NCI which were associated with an Ectromelia outbreak. Safety cabinets and related equipment were tested both at the Middle America Research Unit in Panama, and the Rocky Mountain Laboratories in Hamilton, Montana.

There was a marked increase in requests to ESB to share its expertise to the outside community. Professional and technical advice was provided to other governmental organizations of both this and foreign countries, the university research community and private institutions. Staff lectured at several universities and one international technical symposium on the many aspects of the

ESB program. The NIH Biohazard Safety Guide and the Laser Safety Manuals were developed during the year. The Branch provided technical assistance to the Assistant Secretary of Health, DHEW, by reviewing and assessing the health aspects of many guidelines proposed by the Environmental Protection Agency.

Pollution control activities continued as a major Branch program. Pollution of the NIH stream on the Bethesda campus has apparently been brought under control, as major contaminating sources have been eliminated. Water pollution control activities at the NIH Animal Center continued. The Sewage Treatment Plant experienced operational difficulties during the year, as did the automatic water quality monitors. Noise control developed into a time-consuming program because of new federal regulations. The chemical waste disposal program was developed to the point that the NIH treatment facility is under contract for renovation. A contract was initiated for disposal of chemicals which cannot be handled on NIH premises. The 870 chemical fume hoods were surveyed under contract to the DOW Chemical Company.

General environmental health projects continued with an emphasis on animal room facilities, food surveillance, and solid waste control.

The contract to construct the Tri-Services Incinerator was cancelled and negotiations were begun with Montgomery County, Maryland, for the development of a Medical-Pathological Incinerator by the County to serve NIH and other medical research facilities within the County. Branch staff expended considerable time working with Montgomery County officials and the staff of their engineering consultant firm.

A variety of environmental studies was undertaken. The research contract with the University of Minnesota to study research water quality requirements was completed in June. Other projects included an assay of biological contamination caused by small room humidifiers, analytical procedures for trace quantities of Freon 113 in biological materials, disinfection methods, and the handling and reprocessing of laboratory glassware.

The training effort of the Branch was increased in several areas. A literature review entitled "Biological Laboratory Hazards" was developed and distributed quarterly to Laboratory and Department Chiefs at NIH. Approximately 150 research and technical staff of various institutes attended seminars on The Theory, Operation and Use of the Laminar Flow Biological Safety Cabinet. Of particular note was a cooperative effort with other NIH safety groups in the development of a series of safety posters and accompanying information in the NIH RECORD. An NIH sponsored short course on Introduction to Biological Laboratory Techniques was offered to summer employees. ESB personnel received 1,007 hours of training at designated short courses or classroom experience at local community colleges and universities. Three COSTEP trainees worked in the Branch.

Improvement of human relations continued to receive Branch attention. The Branch Human Relations Committee was effective in restructuring both the employee appraisal of supervisors, and the mid-year employee appraisal techniques. The Committee was of valuable assistance in educational programs prior to the annual employee appraisal. ESB was fortunate in having a staff member selected as Chairman of the Division Human Relations Committee.

II. BRANCH PROGRAMS

A. Objective

The Environmental Services Branch objectives at NIH, Bethesda, Maryland, and field station facilities are:

1. To locate and solve environmental problems.
2. To assure a safe, compatible environment for patients, staff, and the surrounding community.
3. To promote an environment conducive to a quality research program.

B. Current Programs

The Branch objectives were attained through the following closely coordinated program areas:

1. Biohazards and Contamination Control

The biohazards and contamination control program is designed to promote a safe environment for personnel and to protect research work at all NIH facilities in Bethesda and in the field. There is a regular surveillance of potentially hazardous laboratory and animal room areas, control equipment, and facilities. Consultation is provided on a case-by-case basis for laboratory arrangements needed to protect the investigator and the public.

2. Industrial Hygiene

The industrial hygiene program recognizes, evaluates, and controls environmental factors and stresses which may cause illness or significant discomfort among workers or citizens of the community. Gaseous and particulate air contamination (including air pollution) potentially or actually generated at NIH are major surveillance activities. Problems of noise, temperature extremes, and non-ionizing radiation are also investigated and resolved.

3. Hospital Environmental Control

The hospital environmental control program in the Clinical Center is designed to protect patients, employees, and visitors from environmental influences which may be unsafe, unhealthful, or uncomfortable.

4. General Sanitation and Sanitary Engineering

The general sanitation and sanitary engineering program is concerned with basic environmental factors affecting the health of NIH employees, visitors and the quality of the research environment. These factors include food sanitation, water supply, solid and liquid waste disposal, housekeeping practices, pesticides, and water pollution control.

5. Environmental Studies for Support of Research and Patient Care

Continuing environmental studies are conducted as a necessary adjunct to surveillance and consultation activities. Studies are oriented to environmental systems and problems; evaluation of new equipment and methods; quality glassware, animals, and water; environmental stresses related to light, heat, noise, food, water, and waste; and the identification of environmental contaminants.

6. Training

Training to promote job effectiveness is provided for ESB personnel and staff members at NIH. This training is particularly related to environmental control devices and practices in the general research environment which require special training for proper operation and handling.

C. Program Progress and Accomplishments

1. Biological Control

Major program emphasis continued in the area of consultation with NIH research personnel in assessing potential biological hazard problems, equipment use and procurement. Laboratories working with potentially hazardous Class III and IV agents were surveyed. Most notable was the review of laboratory facilities for compliance with the NIAID "Memorandum of Understanding and Agreement" for the safe handling of Adenovirus Type 2 - SV40 Hybrids.

The NIH Specification for Laminar Flow Biological Safety Cabinets was modified three times. These modifications covered the areas of dimensional tolerances, human engineering factors, velocity standards and test procedures. Materiel Management was informed by the General Services Administration that NIH could proceed with the development of a Qualified Products List for this equipment. When the QPL for the laminar flow biological safety cabinet is operational, procurement time for cabinets will be shortened by eighty to ninety days. ESB served as technical advisors to Materiel Management for the laminar flow biological safety cabinet testing and evaluation and in the review of procurement documents with respect to biological safety. The number of laminar flow biological safety cabinets in use at NIH increased from two hundred forty to three hundred fifteen.

Major decontamination projects included nine laboratory rooms; a primate house and barn at the Patuxent research facility, which had been vacated by the NINDS research program; eighteen rooms in Building 14C, which were converted from conventional mouse colonies to barrier derived mouse production; and an animal room in Building 37, which was associated with an Ectromelia outbreak.

The biowaste treatment system for the 5C corridor laboratory "isolation suite" in Building 36 was challenged with bacterial spores to determine the effectiveness of the treatment. This testing was performed after several modifications had been made to improve the overall operation of the system.

The Building 41 exhaust plenums were decontaminated for the Plant Engineering Branch to modify the filter banks and replace HEPA filters. Existing HEPA filters had been in use for approximately four years. Following the work, the installation was leak tested and certified. Filter frame holders in the exhaust plenum at MARU, Panama, were also modified and new filters installed. Testing of safety cabinets was performed at MARU and at Rocky Mountain Laboratories, Hamilton, Montana.

Requests for professional and technical advice from other governmental organizations and private institutions has shown a marked increase. Staff members are involved with committee work for such associations as the National Environmental Health Association and the Health and Safety Committee of the American College Health Association.

A contract has been awarded for the construction of a decontamination chamber to be located on the third floor of Building 13. The facility will be used to decontaminate equipment to be repaired or surplused.

The contract for testing and maintenance of the biological safety cabinets and other bio-control systems was continued. A contract was also negotiated for the development of the NIH Biohazard Safety Guide.

2. Industrial Hygiene

The Industrial Hygiene Program was responsible for initiating and collating the NIH response to the carcinogen control regulations as published in the Federal Register in January 1974 and in response to departmental directives. A questionnaire was devised and distributed to investigators by institute Scientific Directors. Reporting was greatly facilitated by use of a Wylbur terminal. To achieve complete compliance next year with some of the regulations, it will be necessary to contract for laboratory surveys to provide ESB with discrete data.

A major accomplishment was the completion of the chemical fume hood survey. Eight hundred and seventy hoods were surveyed under contract with the DOW Chemical Company. Their report was evaluated and work requests are in process to correct observed deficiencies. This survey will be performed annually in the future.

The Laser Safety Manual will be completed.

An increased number of noise evaluations were performed at the request of various institutes and divisions for the purpose of controlling occupational hazards and for assessing problems of interference with efficiency and performance (a number of NIH employees have filed claims for hearing losses as a result of noise exposure). The energy situation has resulted in more temperature, humidity and lighting problems being brought to ESB's attention both by the individuals concerned and the Employee Health Service.

The problem of filtration of exhaust air to remove small quantities of iodine-131 from the air before its discharge to the outside received full attention this year. Design of one special installation in Building 7 for Dr. Robert

Purcell, NIAID, was completed. Work continues on finding a more general solution for the many other investigators at NIH who function in limited space and with limited capacity exhaust systems.

3. Hospital Environmental Control

This program did not function as a planned operating effort for the first time in several years due to the resignation and subsequent abolishment of the hospital sanitarian position. Services to the Clinical Center continued on a request basis with most activities involving routine check of various sterilizing systems and request assistance to general problems relating to surveillance of humidifying and anesthesiology equipment, and surveillance of housekeeping procedures and sanitation problems in critical areas such as the operating rooms and intensive care units.

4. General Sanitation and Sanitary Engineering

A detailed sanitation survey was conducted for the Division of Pathology, Bureau of Biologics, to evaluate the animal room facilities for conformance to existing standards and the ability to meet program needs. Several less detailed surveys were conducted for other institutes to determine the degree of compliance with the existing NIH animal room standards. A study was conducted for the Veterinary Resources Branch, DRS, concerning cleaners and disinfectants for animal rooms. The information will be incorporated into a standard operating procedure for the Building 14 animal rooms.

Food surveillance efforts continued on a routine basis. Surveys reflected a general upgrading of the GSI cafeterias with the installation of new equipment such as self-service beverage dispensers, refrigerated sandwich display boxes, and single service cup dispensers.

Solid waste control remained a time-consuming effort. Although the Tri-Services Incinerator has been cancelled, ESB did provide input into the final phase of the impact statement via a study on noise from trucks and other sources with the cooperation of the Army Environmental Hygiene Agency. Although not useful for its intended purpose, the report will help in assessing the environmental impact of transportation noise related to the new County operated incinerator, the proposed alternate to Tri-Services. ESB has consulted on this alternative including reappraisal of the waste container to be used with the County's medical-pathological incinerator operation. As a result a one-way, plastic lined box was selected. The paper bag project, initiated several years ago, continued to make progress; there are now 125 bag holders in use outside of the Clinical Center.

ESB continued to monitor and provide technical assistance to the NIH Animal Center sewage treatment facilities. The sewage treatment plant has experienced several difficulties, the two most prominent being solids bulking and excessive sludge buildup. The Office of Engineering Services will contract with an engineering firm to propose solutions to these problems. The automatic water quality monitors experienced a number of breakdowns during the year, resulting in lost or unusable data, plus lost staff time in troubleshooting.

The greatly reduced number of complaints and ESB observations indicate that most of the water pollution sources have been brought under control with respect to the NIH stream on the Bethesda campus. Continued surveillance of mercury waste from NIH was conducted.

An environmental analysis was made of a VRB proposed outdoor primate breeding facility at the site of the NCI Viral Oncology Unit, NIHAC. ESB has been very active in providing reviews of Environmental Protection Agency draft documents related to the environment for the Office of the Assistant Secretary for Health, DHEW.

The ESB chemistry laboratory continues its work in the area of high purity water surveillance, special investigations and services. Work was completed on several projects.

5. Environmental Studies

The research contract with the University of Minnesota to study research water quality requirements is continuing satisfactorily and will be completed in June 1974. The contract has resulted in new methodology in determining total solids, in high purity water, plus considerable data which will allow the Branch to reorient its program for the surveillance of high purity water systems. The recommendations in the final report will be integrated into program plans.

Two short studies of biological contamination caused by small room humidifiers were completed. Results indicated that unless a very strict regimen is followed, these units can become an additional source of air contamination.

A study of particular interest was development of an analytical procedure for trace quantities of Freon 113 in biological materials. This technique was applied in assisting Dr. Albert Z. Kapikian, NIAID, to identify Freon 113 contamination of a viral antigen material to be given orally to a volunteer group.

The Branch studies on *Pseudomonas* have resulted in over 100 requests for reprints. Six requests for the 51 pyocin typing cultures were filled during the year.

A series of studies are in progress on disinfection problems; the role of *Pseudomonas*, *Serratia*, *Klebsiella* and *Herrellia* in the hospital environment; the microbiology of parenteral infusions and sterilization procedures for critical surgical equipment that are heat sensitive.

The energy crisis of December 1973 provided an opportunity to study glassware handling on the reservation. The problem of sorting and separation has not yet been solved, nor has any effort been made to recycle non-contaminated glass. The study will continue on a more vigorous scale when the weather warms up to permit proper sorting at the disposal site.

6. Training

ESB is cooperating with other NIH safety groups, through the Biohazard Subcommittee on Information and Training, in developing a series of safety posters and other information as an effort to raise the safety awareness level of NIH employees. A literature review entitled "Biological Laboratory Hazards" is distributed quarterly in memorandum form to Laboratory and Department Chiefs at NIH and to other individuals interested in biohazard control at NIH and elsewhere. Seminars were presented during the year on The Theory, Operation And Use Of The Laminar Flow Biological Safety Cabinet, to approximately one hundred and fifty research and technical staff.

The Branch offered a short course, sponsored by NIH, to introduce the summer employee to different biological techniques used in the laboratory. It was successfully completed by all twelve employees.

Considerable amounts of time and effort are devoted to lectures and demonstrations for the nursing staff of the operating rooms, Clinical Center. Staff cooperated with the Veterinary Resources Branch, DRS, in one animal caretaker course presented to personnel from NIH, Walter Reed Medical Center, and Fort Detrick Cancer Unit. ESB is also cooperating with the Grounds Maintenance and Landscaping Section, PEB, OES, in providing a training course for the pest control employees and herbicide applicators.

Lectures on various aspects of environmental health and sanitation were presented throughout the year including "Safety in the Laboratory", presented by the National Institute of Occupational Safety and Health. Other lectures were given at the University of Georgia, Indiana State University, The University of Michigan, and the University of Delaware. Assistance was given locally to the District of Columbia Department of Environmental Health and the Fairfax Hospital. The staff also participated in programs of several professional societies including the American Society of Microbiologists, American Hospital Association, American Public Health Association and the National Environmental Health Association.

ESB personnel received 1,007 hours of training at designated short courses or in classroom experience at local community colleges and universities. ESB seminars were continued to provide "state-of-the-art" information to staff and other interested personnel.

Three COSTEP trainees contributed to sanitation efforts at the NIH Animal Center, the solid wastes program on campus, and certain aspects of hospital sanitation.

D. Problems

The program for surveillance of the Clinical Center's environment and environmental control services to its staff was largely curtailed with the resignation of the Hospital Environmentalist and abolishment of the position to meet reduced position quotas. A realignment of the program to provide "emergency" type services was initiated within the Branch's staff capabilities.

Air handling systems, construction and architectural details of some of the older NIH laboratory buildings make them unsuitable for hazardous biological and chemical work from a safety viewpoint. In addition, the research is vulnerable to extraneous environmental contamination. This situation has become more critical due to space shortages. As a result, some laboratory work was relocated on a temporary basis to completely unsuitable space. An example of this is location of laboratories in the 13 North Patient Care Area. This space is in close proximity to patients and totally unacceptable with respect to the air handling and other laboratory requirements.

Staff reports indicate an increasing degradation of environmental sanitation of the NIH buildings and grounds. Buildings in particular need of improved sanitation practices are 6, 10, and 13. Basic problems are associated with the lack of adequate numbers of staff for the central service organization; i.e., housekeeping, plant maintenance and buildings and grounds.

E. Program Plans

Increased contracting will be utilized to accomplish Branch objectives in FY 1975. In particular, a service contract will be executed to help assure compliance with the OSHA chemical carcinogen regulations and infection control guidelines. A similar service contract will be executed to provide assistance and surveillance of biological laboratories working with Class III agents. Two other service contracts will relate to stream pollution control programs on Broad Run at NIHAC. One contract calls for the maintenance and service of the automated water pollution monitors, and the second will assess the sampling activities of ESB and provide a water quality index on which future pollution evaluations will be based. Contracts for monitoring chemical fume hoods and laminar flow biological safety cabinets are continued.

ESB will initiate an Emergency Issuance Exchange Program for laminar flow biological safety cabinets about mid-fiscal year 1975 with an initial purchase of eight cabinets. Emergency need for these cabinets will be justified by the I/D Scientific Director to the Director, DRS, before a cabinet will be issued. This program should help eliminate the six-month waiting period before a cabinet is received, when the investigator may continue working in either marginal equipment or on the open bench.

Posting laboratories with biohazard signs will be updated in the coming year.

Three administrative actions are planned. They are: return to the management by objectives system at the staff, section and Branch level; revision of the Branch data reporting system; and establishment of Branch operation procedures relating to the day-to-day technical programs of ESB.

F. Publications

Oviatt, V.R.: Environmental Control. The Hospital Engineering Handbook, Chapter 7, Chicago, Illinois. pp. 101-116, March 1974.

Gates, A.S., Jr., Wilkinson, T.K.: Disposal of Exhaust Air From Buildings. Proceedings of the 26th Annual Conference on Engineering in Medicine and Biology, Minneapolis, Minnesota. 15:220, 1973.

Karamian, N.A.: Improved Separatory Funnel. Analytical Chemistry. 45:2154-2155, 1973.

Karamian, N.A.: Polytetrafluoroethylene Tubing. American Laboratory. 5:11-14, 1973.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1973, through June 30, 1974

LIBRARY BRANCH

Ruth C. Smith, Chief

I. SUMMARY

The review of personnel and services in all areas of the Library, initiated in May when the Branch Chief entered on duty, was continued. A substantial acquaintance with the entire Library operation was achieved. Some Library activities were identified to be given priority for development, improvement or expansion for more effective Library support of the NIH research effort.

The suit of Williams and Wilkins Company against the Government for alleged copyright infringement relating to the photocopy service of the NIH Library and NLM was decided by the Court of Claims in favor of the Government in a four to three decision. The publishing company is appealing the Court of Claims decision to the Supreme Court.

The Library Advisory Committee met three times during the year. Under the Chairmanship of Dr. John S. Finlayson, BB, the membership remained the same, except that Dr. Stanley A. Robrish, NIDR, replaced Dr. Howell O. Archard.

The monthly listing of books, journals, and other literature added to the Library's collection is now issued as a memorandum from the Librarian. Translated articles are also listed.

A Scope and Coverage Committee was appointed to draw up a plan of action to formulate a Library policy for scope and coverage of literature acquired for the Library collection. The first step, delineation of current B/I/D research and administrative needs through analysis of published programs, has been completed.

Completion of a study on the comparable value of a card catalog vs. a book catalog for use in proximity to the book collection on the Lower Level was followed by an investigation of costs for duplicating cards in the Library's catalog.

Job restructuring was initiated in the Library as an outgrowth of a recommendation by the NIH Job Restructuring Team. The objective is to establish a career ladder of bridge positions whereby a qualified nonprofessional Library Technician could progress in a planned program of on-the-job and academic training to a professional position of Technical Information Specialist.

A new position was created to provide special attention to nonprint media resources. A nonprint collection will be organized, developed, and operated for NIH investigators.

Site surveys of automated circulation procedures in area libraries and literature studies have been made by Library staff. A management study has been proposed to determine the feasibility of implementing an automated system in the Library's Circulation Unit.

The Library participated in the NIH celebrations of Black History and Native American Weeks. The Branch Chief, a member of the NIH Minority Cultural Program Committee, served as a session Mistress of Ceremonies during Black History Week. Exhibits prepared by Library staff for each program were displayed in the outside corridor. High school students participating in the programs were given tours of the Library.

An effective training program for professional and all other staff members contributed to higher quality service to the NIH investigators, to keeping abreast of new developments in Library science, to administration and human relations, and to maintaining employee interest in further training.

A "brown bag" lunch discussion meeting was held by the Human Relations Committee. The Committee also launched a successful drive in the Library for food contributions for an employee on extended leave due to illness.

II. BRANCH PROGRAMS

A. Objectives

The primary mission of the Library Branch is to operate an efficient, comprehensive library in support of NIH scientific, medical, and administrative programs. Activities of the Library include selection, acquisition, organization, maintenance, and circulation of literature pertinent to the programs; operation of a photocopy service; provision of interlibrary loan service; provision of informational, reference, and bibliographical services; provision of Library services advisory assistance; and provision of a translating service for foreign scientific and medical literature. To fulfill its mission, the Library is responsive to changing literature needs of the NIH investigators; is knowledgeable of current developments in manual and machine methods of communication and information retrieval, and is alert to adjustment of procedures for improved library services.

B. Current Programs

Technical Services

The Acquisitions staff provides for the acquisition of books, journals, technical reports, and nonprint materials by purchase, gift, and exchange which have been selected as pertinent to the scope of the Library. The staff is responsible for the maintenance of accession records through input to automated systems used by the Library and for the preparation of completed journal volumes for commercial binding. Computer printout includes daily and monthly cumulated listings of current journals and their holdings and weekly listing of books on order or in preparation.

The Cataloging staff organizes the acquired literature through classification, cataloging and subject heading, and processes it for inclusion in the collection. The staff is responsible for the maintenance of the Library's catalog and the maintenance of catalog records for journals through input to the automated systems.

Readers Services

The Circulation staff provides a charging system, making available books and journals. The staff issues Library Identification Cards; operates the Library's security system; provides an overdue recall system; issues Page-masters; and makes assignments to locked study carrels.

The Interlibrary Loan staff obtains from other libraries literature required by NIH investigators which is not included in the collection.

The Readers Services Section is responsible for developing, maintaining, and servicing a collection of library material in nonprint media pertinent to the scope of the Library and for providing equipment for its use.

The Stacks and Copy Service staff maintains the stacks, carrels, reference and Reading Room areas and reshelves books and journals to facilitate access by the Library clientele. A copy service is provided which allows greater use of the Library's journal collection.

Reference and Bibliographic Services

The Library Services Adviser Program provides an integrated response to the information needs of the NIH scientific community. This may consist of utilization of external resources in addition to the resources and services available in the NIH Library; such as specialized information centers, computerized information retrieval systems, and clearinghouses. The Reference staff supplies ready response to questions, verifies citations, and compiles short reference lists upon request. Its staff receives inquiries at the Reference Desks in the Upper and Lower Level Reading Rooms and by telephone. Reference Librarians answer difficult reference questions and compile literature searches as requested. They serve as selectors for Library acquisitions by continually searching for literature pertinent to the scope of the Library. They also maintain the collection of basic Reference Books. The Section staff provides bibliographic assistance with experienced searchers to conduct requested medical, chemical and biological computer searches through National Library of Medicine's MEDLINE, Chemical Abstract's Chemical and Biological Activities (CBAC) and Biological Abstract's BioSciences Information Service (BIOSIS).

Translating Service

The Translation Unit provides oral, recorded, and written translations as requested. Oral translations are emphasized in-house, and a written translation service is provided through contractual firms.

C. Program Progress and Accomplishments

Technical Services

Several steps were taken to provide more effective assistance to the Library clientele in locating literature. The Library's catalog was separated into two sections, an author/title section and a subject section, for easier use. Plans were completed for the establishment of a duplicate catalog near the book collection on the Lower Level to provide needed information on location. An outline of the Library of Congress classification schedules covering subject areas pertinent to NIH research interests was posted on the Lower Level bulletin board adjacent to the book collection.

Significant progress was made in job restructuring due to cooperative efforts of members of the NIH Job Restructuring Team, the Library's Personnel Generalist and Library management. The objective was development of a planned progression of career ladders with on-the-job and academic training whereby a qualified Library Technician could move over a period of years to a professional position as Technical Information Specialist. Further work on the project has been postponed until a proposal for a major reorganization of the Section is approved.

All current and noncurrent journals in the Library's collection are listed together with their holdings beginning with the March issue of the PHILSOM printout. Organizing and coding the holdings input for the noncurrent journals required one year to complete.

The FY 1974 contract for journal subscriptions was again awarded to the F. W. Faxon Company. The DHEW binding contract was awarded to a new company, Wert Bookbinding Inc. of Middletown, Pennsylvania. This required recoding the binding data changes for input to the PHILSOM journal control system to obtain computer-produced Binding Control Slips compatible for the new binder.

The Library provided professional cataloging assistance to the Library Technician in charge of the Division of Research Grants Library.

Representatives from several New York libraries which are instituting an independent network using the Washington University Medical School Library's PHILSOM journal control system visited the NIH Library in October and November. They were interested in observing the PHILSOM system in action and discussing system-related problems encountered by the Library. The visitors represented the Medical Library Center of New York, Cornell University Medical College Library, and the Library of the College of Medicine and Dentistry of New Jersey at Newark.

Readers Services

Registration for the new NIH Library Identification Cards began in mid-summer. After September 5, the blue ID Card was invalid and NIH employees were required to use the new red Card to obtain Library services.

The Library operated throughout the year with insufficient equipment for effective Library Copy Service. The equipment installed in FY 1973 on a 90-day trial period proved inadequate for required continuous use. With one request disapproved by DHEW, it is hoped that a new justification for obtaining additional equipment will be approved so that this important service to NIH research may be efficiently continued.

New drawers were installed in the Circulation Desk to accommodate the trays containing the book and journal charge files placed on open desks when the request form was increased in size. Easier access to the files was provided the Circulation Desk staff in responding to inquiries and performing charging procedures.

The entire book collection and a portion of the journal collection on the Lower Level were shifted to relieve crowded sections and make possible shelving of newly acquired and returned volumes. This project was given priority by the new supervisory Library Technician in the Stacks and Copy Service Unit serving as Acting Head during the extended illness of the Unit Head.

Effective in August, the National Library of Medicine reduced the number of interlibrary loan requests it will accept from the NIH Library from fifty to twenty per day. An NIH Library employee was regularly scheduled 50-60% of his time to help process NIH Library requests at NLM.

Due to the energy crisis, the Library was requested by NIH Administrative Services to use NIH Vehicle Dispatch for pickup and return of interlibrary loan material and for pickup of priority new books from area libraries and bookstores. Use of government automobiles by Library messengers is limited to pickup and delivery to the National Library of Medicine, Division of Computer Research and Technology and pickup from the Library's book boxes on the reservation.

The Section was given the responsibility for a new Library activity, the organization, development and operation of a nonprint media collection to support NIH research. A Librarian was assigned in March and progress was made in determining the basis of the new service.

A study of the use of the coin-operated copying equipment located in the Library indicated that a considerable number of NIH employees use these machines in the evenings and weekends when the Library Copy Service is not in operation.

Reference and Bibliographic Services

A Reference Assistance Desk was reinstated in the Lower Level Reading Room area to receive reference inquiries from Library users. This station eliminates the need to go to the Upper Level for assistance. An uptrend in reference service continued during the latter part of the fiscal year.

Approximately seventy NIH investigators responded to the Library's announcement in the NIH Record of its MEDLINE orientation/demonstration. Sessions were conducted by the Library searchers in July and August.

The number of requests by NIH investigators for automated bibliographic searches in the biomedical field continued to increase. In addition to medical bibliographies obtained through National Library of Medicine's MEDLINE, the Library now provides NIH scientists with bibliographic searching services, both recurring and retrospective, in chemistry through Chemical Abstract's automated system CBAC (Chemical and Biological Activities) and current awareness in biology and related fields through Biological Abstract's BIOSIS system (BioScience Information Service). The Library's professional staff prepares individual profiles indicating the necessary subject parameters for each request.

Since MEDLINE searching requests continue in high demand, arrangements were made with the National Library of Medicine for a second access code to its computer through the NIH Library's WYLBUR terminal at minimal fee. The Technical Services Section scheduled use of this terminal to avoid conflict with WYLBUR acquisition and cataloging programs. Technical Services Section is able also to access NLM's CATLINE and SERLINE via this terminal for cataloging and acquisition information.

The Section Chief participated in NLM's Region IV MEDLINE Workshop on November 1-2, speaking on a panel on "Analyst-Requester-Data Base Interpretations."

Translating Service

Contact translating services for written translations, which are not now limited by the Library's budget, increased substantially in the first complete year of direct charges to the B/I/D's. Quality control for the completed translations is provided by the Library. Oral translations continue to be emphasized in-house.

Training

The FY 1974 Branch Training Program was developed through individual discussions between the Section Chiefs and their employees. Proposals were made for beneficial employee development in the present job and for more effective use of the employee in the Library. Some three hundred fifty man-days were devoted to employee participation in academic, administrative, technical and in-Library training courses and workshops. One Library Technician received the Certificate of Accomplishment for Library Technicians granted by the U. S. Department of Agriculture Graduate School upon completion of an organized course of several years' study. One employee continued special training relative to the Basic Adult Education program. Two employees were enrolled in the NIH/FCC Upward Mobility College and one in Federal City College.

Exhibits

Exhibits prepared by the Library staff and displayed during the year covered the following topics: Library Services, History of the Public Health Service, What is CBAC?, Acupuncture, Black History Week, Native American Week, and National Library Week. Assistance was received from the Medical Arts and Photography Branch, and Mrs. Kathleen Snowden, Veterinary Resources Branch, loaned unusual wood carvings, jewelry, and some rare historical journals for the Black History Week Exhibit.

D. Problems

Downtime and poor product quality of the present photocopy machines continue. Past efforts to obtain new machines to meet the heavy demand have been rejected. Additional justifications for the requested equipment have been submitted.

The level of the humidity on the lower level of the Library detrimentally affects the Library's main collection of books and journals. Higher humidity developed when the chilled water in the cooling system was cut off during the energy crisis.

Increased efforts are planned to resolve or eliminate personnel problems that remain in some Sections.

E. Program Plans

Completion of a Scope and Coverage Statement will provide much needed governing rules for developing the Library's book and journal collections.

When approval of the planned reorganization of the Technical Services Section is received, careful attention will be given to orienting and training the staff in the substantial procedural changes to effect an orderly transition.

Development and implementation of an automated circulation system will provide a more efficient service to Library clientele and will provide better control of the Library's collections.

After establishing specific requirements of NIH researchers, a nonprint media collection will be developed to expand the present microfilm and microfiche holdings of the Library. Equipment needed in its use will be acquired, such as projectors, screens, playback units, tapes, filmstrips, and slides.

Conversion of the subject headings used in the Library's catalog to identify and locate medical books and journals held in the collection will provide the investigator with the specialized medical terminology used by the National Library of Medicine. Library of Congress headings will continue to be used for material in other subject fields.

Anticipated completion of a duplicate card catalog adjacent to the book collection on the Lower Level will facilitate access to the main book and journal collections.

Arrangements will be made with the National Library of Medicine for a second MEDLINE terminal to meet search demands and to use CATLINE in converting to NLM's medical subject heading (MeSH) system.

F. Publications

Smith, Ruth C.: SHARP: Experiences in Library Automation. Special Libraries 65: 61-65, 1974.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1973 through June 30, 1974

MEDICAL ARTS & PHOTOGRAPHY BRANCH

Mr. Arthur F. Moore, Chief

I. SUMMARY

Demands for MAPB services remained high. With a completely renovated Photo Lab, requests were serviced within five days and the Branch is committed to the reduction to seven days for photomicrograph and photomacrograph services by the end of FY - 75. The newly named and reorganized Design Graphics Section has cut production 10 percent in reprint material, however, design and delivery of exhibits increased 100 percent. Medical Illustration continues a substantial steady output. MAPB increased its use of outside contract services by 26 percent. With new equipment and facilities, Branch continued to improve and broaden its skills to meet increased program demands with dispatch and high morale.



II. BRANCH PROGRAMS

A. Objectives

The objectives of the Branch are to provide consultation and production services to the NIH; to visually communicate program effort and research results; to provide knowledge, skills and techniques in visual design, medical art, applied arts, still photography and cinematography for solving problems of recording, communicating and presenting research activity; and to investigate, develop and apply new visual techniques.

It is also the objective of the Branch in meeting NIH research program demands to provide professional services, competitive with commercially obtainable services at the lowest possible cost, and to develop specialized capabilities, particularly in graphic presentation, still photography, cinematography, and medical arts, tailored to NIH needs.

The Branch monitors procurement of art and photography services by outside contract, serving as a technical adviser in obtaining needed additional services at the lowest cost consistent with high quality.

B. Current Programs

Programs of the Branch are still and motion picture photography, including photomacrography, photomicrography, cine photomicrography, high-speed cinematography, general photography, and related laboratory services; visual arts production including publications design and general graphics; visual aids including slides, vu-graphs, and other projectables; animation artwork; technical, general and medical illustration; exhibit design; statistical drafting display charts; medical models, and computer-generated graphics.

C. Program Progress and Accomplishments

1. Service Time Acceleration and Graphics Program

The demand for MAPB services remained high. In the Photo Lab, the posted turn-around-time for requests is five working days, however, 20 percent of the work was done in less time on an emergency basis. The scientific photo unit turn-around-time for finished product was 15 workdays with a small amount of work completed more rapidly on emergency demand. This delivery time is excessive and the Branch is committed to reducing the wait from 15 to at least 7 days for scientific photography by the end of FY - 75.

There was a decided demand for more color photography. Black & white photography continued at the same level.

Requests for Medical Illustration remained at a high level.

As a result of DHEW ordered cutback in informational materials, production of booklets, brochures, pamphlets, etc., dropped approximately 10 percent.

This is reflected primarily in the reworking of reprint material. At the same time, approved requests for design and construction of exhibits was up 100 percent.

In the area of Design Graphics, an independent study of all the NIH graphics was conducted by the National Endowment for the Arts. Their findings concluded NIH graphics lacked coordination with a resultant loss of image to NIH and its component Institutes.

The Branch took positive steps to rectify this situation by initiating a major ongoing plan to develop a well coordinated graphics program to more effectively communicate work being done at the NIH to the scientific community and the public.

2. Operational Improvements

The General Illustration Section was reorganized and renamed the Design Graphics Section to more clearly describe its overall functions to the prospective NIH user. Two of the three units, Graphics and Drafting, were combined under the Graphics Unit to avoid duplication, to gain uniformity of production and to enrich those jobs in the drafting area which, in recent years, have become so simplified as to reduce the work to little more than replotted tracings.

A complete renovation of the Photographic Laboratory spaces was completed, with installation of new highly technical equipment. This allows for increased production, quicker response time, improved quality and morale among the employees.

Photographic end-product prices were revised to reflect a more accurate balance of profit and loss margin. The Section operating costs, reflected in the revolving fund were within 1 percent of the break-even point. Total revenue was in excess of \$404,000.

3. Service Contracts

There was a 26 percent increase in outside contracting. With numbers of Branch personnel remaining static, this figure represents a substantial increase in demand for MAPB services from the NIH community.

During FY - 1974, the Branch streamlined contract service billing procedures, processing them in half the time previously required. However, these actions have only partially accelerated payment to service suppliers which remained embarrassingly slow.

4. Training

Thirteen members of the Branch attended out-of-the-area professional multiple-day seminars. In addition, 24 employees attended 43 separate formal training courses.

5. EEO Developments

Heavy emphasis was placed on continued familiarization of Branch employees with the EEO. This was accomplished with groups of employees in meetings with EEO-HRC representatives. Many suggestions were made directly to the EEO officers by the employees and many were implemented. Similar meetings were held with first line supervisors, and EEO-HRC representatives. Eight employees from the four sections of the Branch attended the two-day DRS-EEO Seminar in May.

6. Labor Relations

A new two-year labor management agreement was negotiated between the MAPB and AFGE Local 2419. Negotiations were conducted in a cooperative manner and the MAPB has had no problems working within the agreement. The MAPB considers it an honor to have both the President and Vice-President of AFGE Local 2419 on its staff.

D. Problems

The Branch was increasingly dependent on outside quality contractors to meet the demands of the NIH community. MAPB has identified a number of purveyors of high quality services, however, one-by-one these contractors refused to serve the Branch because of the long time it takes the NIH to pay them for work done. This situation leaves the MAPB increasingly vulnerable in meeting the mounting demands from its clients.

There is also a critical need for the NIH community using MAPB services to allow more lead time for planning and execution of their audio-visual material. The Branch has extensive expertise in planning and conversion of raw data into effective multi-media presentations. This counsel is readily available in all areas of MAPB, or on location, and should be used earlier and more frequently.

E. Program Plans

The Medical Arts & Photography Branch will pursue the development and implementation of a systems approach to upgrading the NIH Graphics Program. It will continue to improve, enlarge, and extend its services and will seek more persuasive ways to acquaint the NIH community with its skills. The Branch will continue to emphasize the necessity of early counsel and planning for optimum results.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1973, through June 30, 1974

Veterinary Resources Branch

Dr. Robert A. Whitney, Jr., Chief

I. SUMMARY

The Veterinary Resources Branch provides NIH investigators with living models and life support systems for biomedical research. The Branch also provides facilities and services related to the use of these models and systems.

VRB service functions continued to increase to meet demands of expanding intramural BID programs, although branch personnel ceilings have been reduced 18 percent over the last six years.

Increased service with decreased personnel was accomplished by extensive use of overtime, improved animal production methods, automated processing of glassware and production of media, limited use of temporary positions and, of most significance, contracting.

The Rodent and Rabbit Production Section was reorganized and renamed the Small Animal Section. The new organization is designed to be more efficient in responding to BID requirements for rodents and rabbits produced intramurally and from contract sources.

A Catalogue of NIH Rodents was published. Characteristics of more than 100 strains and stocks of rodents and rabbits maintained in the VRB genetic repository are described in loose-leaf notebook form. Approximately 150 breeding nuclei of VRB strains of mice were provided to the international biomedical research community.

Investigators' requirements for VRB produced rodents and rabbits increased and total issues remained at about 500,000 despite a reduction in permanent personnel; however, an imbalance of temporary employees was utilized in some areas to maintain adequate production levels. Issues of noninbred animals from contract sources decreased.

The importance of maintaining the genetic pool of VRB noninbred stocks was demonstrated to be essential for the continuance of effective testing of biologics. VRB colonies of mice now originate from hysterectomy-derived, barrier-maintained breeding stock. New pathogen-free colonies were established this year and the old conventional colonies phased out.

While rodent, rabbit, and cat production dropped, laboratory reared dogs, timed-pregnant nonhuman primates, and ungulate production increased. Contracts were used to supplement canine, primate, and ungulate production as well as rodent production.

Outbacks in rhesus monkey exports from India in 1974 prompted VRB to initiate domestic breeding programs. A new facility at Perrine, Florida, was obtained from the Environmental Protection Agency and is being stocked with over 700

rhesus breeders. Contracts are also being negotiated to initiate other domestic breeding colonies to produce 500 or more rhesus monkeys per year for use in NIH intramural research.

Tissue culture and media production decreased 6 percent. Glassware issues decreased 12 percent. Personnel reductions and increased use of disposable supplies contributed to this reduction, which was largely due to the decision to stop supplying two major NCI contractors with media.

Surgical activities and support have stabilized at 800 procedures per year. Surgical facilities are now used at maximum capacity.

Experimental animal holding for dogs, which has long been over capacity, was, in part, contracted. With the Phase I renovation of Building 14D, protected facilities are available for holding 1,000 nonhuman primates. Over 1,700 primates will be held in this building on completion of Phases II and III renovations.

The Animal Disease Investigation Service was reorganized to ensure rapid response to requests. The number of calls made to the BID's increased by 22 percent, from 150 to 183. They involved consultative, diagnostic, and therapeutic activities and included rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls are varied and involved all Institutes. This service, well received by the BID investigators, has gradually increased in scope. It has been mutually beneficial to investigators and to the VRB professional staff in providing an overview of laboratory animal facilities and practices at NIH.

II. BRANCH PROGRAMS

A. Objectives

The primary objectives of the Veterinary Resources Branch are:

1. Issuance of research animals, animal biologics, tissue cultures, tissue culture media, bacteriologic media, and laboratory glassware.
2. Maintenance of a centralized genetic repository of valued animal strains for the scientific community.
3. Provision of facilities and professional staff for experimental surgery to include postoperative care and roentgenography and other special procedures.
4. Maintenance of animals during experimentation and collaborative research support.
5. Acquisition of information, through research, on animal health, care, and husbandry, and identifying animal models for human diseases.
6. Provision of consultative services on animal health and husbandry, use of experimental animals, tissue cultures, and bacteriologic media.

B. Current Programs

1. Research Animal Production

Rodents, rabbits, dogs, cats, and primates are bred and reared in the Branch's colonies. Some are characterized genetically and some are microbiologically defined. Care is taken to maintain the genetic integrity of inbred strains and minimize inbreeding or random bred stocks. Germfree and specific pathogenfree (SPF) rodents are produced for intramural research programs requiring them and for replacement breeders to enhance the health status of production and genetic colonies.

2. Research Animal Procurement and Conditioning

Nonhuman primates, dogs, cats, ungulates, and feral animals are purchased and conditioned. These animals are not well defined genetically or microbiologically. Although they are of lower quality than NIH-bred animals, they are satisfactory for certain studies. These animals are quarantined prior to release for use in research programs. During the quarantine period they are given appropriate immunizations, tested for a variety of infectious agents and are treated medically as required.

A colony of blood group CEA 1, 2 and 3 negative canine donors is maintained for the production of normal canine blood for research use. Ungulate animals are maintained for the production of antisera, normal blood or tissue specimens.

Facilities are provided for investigators to perform experimental surgery on ungulate animals. They include modern equipment for restraint, anesthesia, and physiologic monitoring under aseptic conditions. Postoperative care is provided and radiographic facilities are available.

Ungulates are held under observation for NIH investigators during investigative studies. Physiological sampling and specimen and collections are provided in association with these studies.

Noninbred rodents and rabbits are procured through contracts to supplement in-house production. They are delivered directly to NIH investigators. Quality control of these species is maintained through monitoring of the various producers' facilities and operations by Branch staff members.

3. Tissue Culture and Media Production

Several continuous cell line tissue cultures are maintained, propagated, and produced in large volumes to supplement I/D requirements not met by commercial sources or individual laboratory preparation. Media for the culture of bacteria, fungi, and tissue cells are produced to meet the needs of NIH investigators. A stringent quality control program insures that only high quality products free of contamination and true to formulation are issued. As a service to investigators, valuable cell lines are frozen and stored for long-term preservation.

4. Processing Laboratory Glassware, Animal Cages, and Miscellaneous Items

Laboratory glassware is decontaminated, sorted, cleaned, inspected, plugged, wrapped, sterilized, and issued to NIH investigators. The overall operation includes processing of used glassware received from investigators and the introduction of new glassware from replacement stock. In addition to cleaning animal caging for its own programs, the Branch furnishes cagewashing services to investigators in the Clinical Center and the Buildings 14-28 complex. Clinical Center rubber-backed carpets are also washed. A service is provided for ethylene oxide sterilization of heat labile patient and laboratory equipment from the Clinical Center and other I/D's.

5. Animal Biologics Production

A dog blood donor colony is maintained for the production of Canine Erythrocyte Antigen (CEA) 1, 2, & 3, formerly A-negative, blood for research use. Ungulates are maintained to produce a variety of antisera, blood, and tissue specimens for investigators.

6. Genetic Repository and New Animal Models Program

Genetically defined rodents that are valuable models in biomedical research are derived and maintained to support I/D requirements and serve as a genetic repository for the international scientific community.

7. Experimental Surgery, X-ray and Related Activities

The surgical facilities are primarily available for the use of BID investigators; however, frequently, surgery is performed by veterinarians assigned to the section in support of BID programs in the development of surgical animal models. In addition, staff veterinarians provide surgical and clinical veterinary care to laboratory animals as an essential part of their responsibility to assure optimum health of these government-owned animals. Assistance to BID investigators is continuously provided in anesthesiology, surgical support, diagnostic radiology, and postoperative care of animals.

The number of surgical procedures has stabilized at approximately 800 per year and the facilities are being used at maximum capacity. No gain is projected for the next year unless constraints in space and personnel are resolved.

Experimental surgery continues to be complex with numerous thoracic, cardiovascular, and abdominal procedures demanding a high level of technical support. Professional and technical assistance to BID investigators increased which resulted in improved surgical animal models and veterinary medical care.

8. Experimental Animal Holding

Dogs, primates, ungulates, and germfree rodents are held for varying periods of observation while under test by NIH investigators. Provision is made for physiological sampling and collection of specimens.

9. Disease Investigation, Research, and Quality Control within VRB

The professional staff consists of persons trained in general clinical veterinary medicine and specialists in laboratory animal medicine, pathology, microbiology, epidemiology, nutrition, and animal husbandry. All efforts are oriented toward improving the Branch's programs by gaining new knowledge through research and monitoring the quality of procured and produced animals.

10. Consultative Services

Information and assistance are available to NIH investigators for solving problems relating to animal experimentation, health, care, and husbandry. Through the Animal Disease Investigation Service (ADIS) "house calls" are made to the I/D's to provide investigators with clinical veterinary services for their research animals. There is also a program to furnish each I/D a comprehensive review of its animal care programs with evaluations and recommendations for improvement. Consultative services on use of tissue cultures and microbiologic media are available.

11. General Support and Management

These basic programs listed above are also supported by Branch-wide administrative and management staff and transportation/delivery service.

C. Program Progress and Accomplishments

About 500,000 VRB-produced rodents and rabbits were issued to investigators, equivalent to the number produced last year. Guinea pig and rabbit production decreased, rat and hamster production remained unchanged, but there was an increased requirement for and production of VRB inbred and noninbred mice. The total demand for VRB strains and stocks of mice was not satisfied by current production levels.

Conventional mouse production colonies were phased out and new pathogen-free colonies established from hysterectomy-derived breeding stock raised in the barrier. The new pathogen-free colonies were initially established in a "clean conventional" building and the old conventional colonies moved to the rabbit building while the former mouse production wing was decontaminated, painted, and converted to a "clean conventional" building. The pathogen-free inbred mouse production colonies were then moved back into the decontaminated building. Most investigator responses to the higher quality mouse were favorable; however, a few are dissatisfied with changed that resulted in alterations in baseline data. Inbred mouse strains have not adapted to the barrier and are being isolated while attempts are made to hysterectomy derive them directly into a "clean conventional" area.

Commercial sources of noninbred mice have proved unsatisfactory for testing certain biologics; therefore, FDA has provided temporary positions to increase General Purpose and NIH mouse production. The Frederick Cancer Research Center (FCRC) continues to rely on VRB foundation colonies as the

genetic base for their rodent colonies. Pedigreed mouse and rat strains are now provided exclusively from a barrier to reduce the possibility of contamination to their colonies. The demand for noninbred mutant "nude" (athymic) mice is increasing due to its immunologic deficiency. Production of this mouse, which is difficult in conventional colonies, has been excellent under barrier and "clean conventional" conditions.

The pathogen-free rat colonies in the barrier continue to have excellent health and reproductive performance although it has been over five years since they were initially hysterectomy derived. The Osborne Mendel and F344/N clean conventional production colonies were contaminated with Sendai virus, relocated in a conventional area, and decontaminated rooms were restocked with barrier animals. The new colonies are Sendai free.

A major effort was made to hysterectomy derive inbred guinea pigs and establish foundation colonies in the barrier. Over 300 term feti have been taken by hysterectomy derivation into germfree and pathogen-free isolators. Maintenance of the young under isolator-defined flora conditions has been successful, but establishing a viable nucleus in the barrier has not. Various combinations of bacteria are being tried to establish an acceptable intestinal flora and various dietary regimes are being used to establish nutrient requirements, growth, and survival rates.

Vegetable supplementation (kale) was eliminated from the diet of the guinea pig production colonies without a noticeable effect on productivity. Simultaneously, the amount of drinking water provided daily to the guinea pigs was increased. Hartley guinea pigs from Edgewood Arsenal were removed from the proposed clean conventional production wing when found serologically positive for Sendai, GDVII, SV5 and H-1 viruses. They continue to show good reproductive performance on an autoclavable open formula diet.

A nucleus of pathogen-free rabbits obtained from Edgewood Arsenal are serving as foster mothers to establish pathogen-free colonies of NIH rabbits in a clean conventional environment. The colony has remained free of Pasteurella and Bordetella infections as well as internal and external parasites; however, Tyzzer's disease has been diagnosed. The C-6 deficient and Netherlands Dwarf rabbits have been successfully established in the new environment as well as most of the defined allotype strains which are being inbred. A small nucleus of the noninbred NIH New Zealand White rabbit is also being hysterectomy derived and foster nursed to retain the genetic base of that colony in a "clean conventional" environment.

Rabbit production was decreased to a maintenance level with the initiation of a contract to provide noninbred New Zealand White rabbits. Techniques are being studied to develop a better defined pathogen-free rabbit.

The Rodent and Rabbit Production Section was reorganized and its name changed to the Small Animal Section. Under the new organization there will be a building supervisor in animal care areas, a cagewash unit, an ordering and contracts office, an administrative assistant, and a professional services group. The Genetics Unit was eliminated as an organizational entity; however,

the role of strain maintenance is expected to be enhanced because of the additional time that will be available to the geneticists for technical matters.

b. Large Animal Production

The canine breeding colony currently consists of 143 bitches and 11 dogs. Culling continues to be directed towards eliminating poor producers and animals with hip dysplasia. The last of four inbred lines of foxhounds was established. The inbreeding colony currently consists of one English and three American (two Walker and one Trigg strain) foxhound lines. Development of these lines is being directed principally towards providing a genetically uniform research dog for NIH investigators by eventually crossbreeding the lines.

A contract was established to breed and provide purebred foxhounds for NIH research at a rate of 400 to 600 per year. Availability of purebred stock from NIHAC and contract sources has reduced the need to rely upon random source foxhounds and permits elimination of random source mongrel dogs as standard NIH research animals.

The cat breeding colony was reduced from 25 to 13 queens and six toms. The projected rate of issue is approximately 150 cats.

The goat breeding herd was expanded from 10 to 16 does and one buck. Goats produced from the breeding herd will be held until approximately one year of age before issue.

c. Nonhuman Primates

A nonhuman primate breeding colony was established at Perrine, Florida. At capacity, it is expected that the colony will contain about 700 adult female rhesus monkeys as well as their neonatal offspring. The facility will have been stocked with at least 250 breeders by the end of FY 1974. Production from the colony will upgrade the quality of rhesus monkeys for research and supplement embargoed supplies of rhesus obtained from the wild.

The timed-pregnant rhesus monkey breeding colony has continued to grow from 165 animals to 270 animals, including 40 rhesus monkeys assigned to NINDS which are also managed as a timed-pregnant breeding colony. Currently, there is a contract with Gulf South Research Institute to provide from 80 to 100 timed-pregnant rhesus monkeys in addition to the VRB breeding colony. The VRB breeding colony is newly developed and, over the past year, 120 pregnant animals were produced and assigned to BID investigators, in addition to 28 timed-pregnant animals delivered by contract. A new contract for timed-pregnant baboons is planned to provide another animal model for pregnancy and perinatal research.

2. Research Animal Procurement and Conditioning

a. Rodents and Rabbits

The total purchase of rodents and rabbits from contractors decreased from 132,500 in FY 1973 to approximately 90,000. There was a decline in acceptance of noninbred mice, rats, and hamsters from contract sources. A contract for Hartley guinea pigs was initiated. However, the contractor was not able to provide sufficient animals to meet NIH requirements. A contract for New Zealand White rabbits was initiated which, thus far, is providing acceptable quality and service. An itemized list of animals purchased on contract are as follows:

Hartley Guinea Pigs--Carworth	2,500
Rabbits--Lab-Rabs	2,500
Sprague Dawley Rats--Taconic	35,000
Hamsters--Lakeview	9,000
Swiss Mice--Taconic	40,000

In addition, VRB arranged for the Frederick Cancer Research Center to supply NIH investigators over 1,300 Hartley guinea pigs, 500 inbred guinea pigs, 2,500 inbred mice, and 150 rabbits.

b. Large Animals

Random source mongrel dogs and random source foxhounds are purchased after 30 days of conditioning by the vendor. Illness and losses among animals have been minimal. The trend in issues of random source dogs of both types declined. Estimates indicate that approximately 800 to 1,000 random source dogs (mongrel and foxhound) will be issued. The contract requirements for mongrel random source dogs will be reduced from an estimated 1,040 (FY 1973) to 150 (FY 1974).

Requests for random source cats appear to be increasing slightly. Projected issues are 700 to 800.

Approximately 550 ungulate animals will be purchased, quarantined, conditioned, and issued. In addition, some 50 domestic fowl including ducks, chickens, and turkeys will be utilized.

The primate quarantine facility entered its second year of operation and is currently filled to capacity. An effort has been made to procure as many large, stock rhesus monkeys as possible so as to be able to fill the needs for breeding stock at Perrine, Florida, and Gulf South Research, and to supply basic NIH needs.

Rhesus (Macaca mulatta) monkey issues are estimated at about 3,575 which represents an increase of about 875 over last year.

Other species of monkeys and apes (M. fascicularis, M. nemestrina, Erythrocebus patas, Saimiri sciureus, Cebus albifrons/apella, Cercopithecus athiops, Papio spp., Aotus trivirgatus, Saguinus oedipus, Callithrix sp., and Pan sp.) contributed small numbers to the overall quarantine and conditioning program.

3. Tissue Culture and Media Production

Based on the first seven months of FY 1974, the number of requisitions processed for tissue culture and media will total 13,000; a decrease of 6 percent from last year. The volume of media produced will be 63,000 liters of bacteriologic media and 65,000 liters of tissue culture media for a total of 128,000 liters. This total represents a 12 percent decrease over last fiscal year, and primarily results from a policy decision to no longer supply tissue culture media on a routine basis to NCI contractors.

Issues of blood agar plates of all types, including horse, sheep, and human blood plates will total 148,000 this year, a 1 percent increase. In addition to blood agar plates, there will be another 378,000 plates of other types for a total of 526,000 plates for the fiscal year. This is a 26 percent increase over last fiscal year.

Issues of tissue culture cells as cell suspension increased 10 percent to a projected total of 206 liters of suspension. This is indicative of a trend toward cells in suspension rather than tubes or bottles of cells.

Tissue culture cell freezing and storage services continued to show increasing popularity with NIH investigators. A projected total of 3,000 ampules of cells will be frozen and over 2,300 ampules of cells were maintained in the frozen cell bank to support research programs. This represents a significant increase of 42 percent over last fiscal year.

Renovations to provide filtered air to the room housing the automatic media bottle filling system are expected to extend aseptic bottling to sterile tissue culture media. This system should eventually lead to almost total automation of media dispensing for both bacteriologic and tissue culture media.

Construction of a separate sterile filling room to house an existing automatic tubing machine has provided a much more efficient operation for this important aspect of media production. It is now possible to carry out sterile production in tubes simultaneously with other types of production.

Further automation of the labeling system is expected to greatly reduce time-consuming manual application of labels to bottles. The new system will be tied in with the existing bottle conveyor after minor problems of synchronization and label specifications are solved.

Several improvements to provide better working conditions were accomplished. An air-conditioned employee lunchroom, which also serves as a Section conference room, was provided. Improved lighting of a windowless main

corridor considerably brightened an otherwise dark and dreary area, as well as making the area safer. Plans for painting and installation of improved air-conditioning for several high-heat-load work areas are underway.

4. Processing Glassware, Animal Cages and Miscellaneous Items

Projected glassware issues to the I/D's totaled 8,124,000 pieces; a decrease of 14 percent over last fiscal year. A projected total of 244,000 cages, racks, and associated pieces of equipment were processed, not including carpets washed for the Clinical Center.

New detergent controls were purchased for cagewashing and glasswashing machines. Hopefully, these controls will reduce the amount of detergent used and also provide more accurate dispensing.

Two new electric dryers were purchased and are awaiting installation. These dryers will be located near the pipette washers and will be used to dry pipettes. The relocation of these dryers will greatly reduce the handling and transporting of washed pipettes.

5. Animal Biologics Production

Domestic turkeys and ducks were used in small numbers to produce normal blood and antisera for specific research projects.

The canine blood donor colony, which consists of 258 dogs, produced an estimated 3,200 units (1 unit=500 ml) of blood.

The RIF-free avian activity was phased out early in the fiscal year.

Biologics production from ungulate animals was stable. Projected production includes 1,500 liters of ungulate blood. The size of the ungulate herd maintained for all purposes increased from 515 to 550.

6. Genetic Repository and New Animal Models Program

Catalogue of NIH Rodents was published. It describes characteristics of the over 100 strains and stocks of rodents and rabbits maintained. These colonies represent the most diversified, multispecies collection maintained in any one facility. In addition to supplying animals for intramural investigators, breeding nuclei from these colonies serve as a resource for the international biomedical research community as many of the stocks, strains, and substrains are not available elsewhere. Over 150 investigators were provided with litters of inbred animals to start colonies and several hundred noninbred animals were provided as breeding stock. Several commercial producers were also provided with breeding stock. Requests were particularly numerous for the hypertensive rat; nude, athymic mouse; and inbred guinea pigs.

A program to assist investigators in obtaining new animal models to meet previously unfilled research needs continued. In some instances, new strains of existing laboratory animals exhibiting unique physiological or anatomic characteristics were used. In others, animals having characteristics required

in a particular research problem were adapted from nature. New models are hysterectomy derived and foster nursed or hand nursed prior to introduction into the NIH colonies. Three new strains were added to the repository at the request of NIH investigators. They are:

Inbred Mice: BALB/cCr
Inbred Rats: Lou/c/WsL
 Lou/m/WsL

The new BALB/c subline was requested by NCI to support production at FCRC. NCI also requested establishment of the additional rat strains and some NCI contract programs are calling for use of VRB colonies as the genetic base.

7. Experimental Surgery, X-ray, and Related Activities

a. Building 28 Facilities

The surgical facilities are primarily available to BID investigators; however, surgery was frequently performed by veterinarians assigned to the Section at the specific request of investigators. Assistance to investigators was provided in anesthesiology, surgical support, diagnostic radiology, and postoperative care of animals.

Surgical facilities in Building 28 were used at maximum capacity. No projected increase is anticipated next year due to limitations of building size and room arrangement unless the surgery suites are moved to Building 14E. There was also a marked increase in the time devoted by Experimental Surgery Unit personnel in providing better technical and professional assistance to investigators conducting research in this surgical facility.

b. Animal Center Ungulate Surgery

Activities in ungulate surgery declined from previous levels. Projects utilizing sheep for intrauterine fetal surgery are expected to be markedly decreased and, possibly, cease. Breeding continued to develop four inbred lines of immunologically distinct miniature swine. Five sows produced 20 progeny this year. A project concerning the possible teratologic effects of feeding blighted potatoes to pregnant sows involves a small swine breeding program and surgery.

Radiographic procedures remained constant with 250 exposures projected.

8. Experimental Animal Holding

a. Primates

Renovations were completed for Phase I of Building 14D with a capacity of over 800 primates. Heavy demands by BID investigators for this space totaled approximately 1,100 primates. To meet these requirements, completion of renovations of Phase II and III are mandatory for the beginning of FY 1975.

This coincides with the programmed renovations of the BoB portion of Building 14D so that a complete primate research holding facility will be available to meet the needs of NIH. A total capacity of 1,750 simian primates assigned to specific research projects will establish this colony as one of the largest primate facilities in the United States. Isolation facilities permitting infectious disease studies in up to 700 animals will also be provided by the renovation.

b. Canine

The population of long-term dog holding leveled at approximately 350 dogs per month. This was achieved through a contract to hold dogs off the Bethesda campus when only infrequent investigator manipulation is required. This permitted a more suitable canine density population per kennel to achieve better animal care management. The south wing of Building 14E was equipped with 22 individual dog runs which currently hold dogs on atherogenic diets.

c. Ungulates

Several species of ungulates were held under observation for NIH investigators during investigative studies. Physiological sampling and specimen collections were provided in association with these studies.

9. Animal Nutrition

VRB-developed open formula rations for rats, mice, and rabbits were used increasingly throughout NIH during the past year without any reported problems from investigators. Purchase of the rabbit ration was approximately 50 percent above the estimated yearly requirements. Based on dollar value, approximately 70 percent of the animal feeds used by NIH are presently purchased via advertised contracts for open formula rations while 30 percent are purchased via negotiated "sole source" contracts. Prior to initiation of the nutrition program, this ratio was 30 to 70 percent for feeds purchased via advertised and negotiated contracts, respectively. An estimated \$40,000 per year was saved as a result of the increased use of advertised contracts.

A contract was established with an independent laboratory to conduct estrogen assays and a limited number of nutrient analyses on samples collected from feeds manufactured for NIH contracts. Objectives were attained without any major problems. The estrogen assay results were uniform while the nutrient analyses indicated considerable variation in the nutrient concentration among production batches of animal feeds. The requirements of this contract were expanded to include nutrient analyses on every sample of feed submitted for estrogen assay. A contract was established to conduct various nutrient analyses on experimental laboratory animal rations. Data obtained from this source was the basis for establishing vitamin levels in open formula autoclavable rations.

Data was accumulated indicating it is not advantageous to feed rats and mice rations containing more than 16 to 18 percent protein for maximum reproductive performance. This is important since ingredients containing high quality

proteins are not readily available and the current cost of each percent of protein is approximately \$12 per ton of finished product.

Considerable progress was made toward formulating autoclavable rations for rats, mice, rabbits, and guinea pigs. Vegetable supplementation of the production colonies of guinea pigs was discontinued.

An increasing number of NIH investigators asked for assistance in formulating and/or obtaining rations for special research projects and in various nutritional studies with rats, mice, and primates.

10. Animal Health

a. VRB Animal Health Problems

An enterococcolitis was recognized as a new disease problem in weanling age rabbits in C wing, causing over 10 percent of fatalities. Culture results indicate that the disease is caused by overgrowth of *Escherichia coli*. Whether this strain of *E. coli* is particularly pathogenic for rabbits or is simply over-populating the intestines of rabbits held in an unusually clean environment is not known. The rabbits in C wing are free of a number of common bacteria of rabbits, including the respiratory pathogens *Pasteurella multocida* and *Bordetella bronchiseptica*. Pneumonia caused by these agents is still a problem in the few remaining "conventional" rabbit rooms (11.5 percent of fatalities). Neonatal deaths accounted for more than 30 percent of losses in rabbits. Findings indicated that most deaths were due to failure of the dam to properly feed or care for her offspring.

Strongyloidosis occurred for the first time in the history of the rabbit colony. The ova and larvae of *S. papillosus* were detected in a composite fecal sample from one room during the weekly coccidiosis surveys. Although an attempt was made to eradicate the disease by frequent testing and killing of affected animals, within three weeks the disease cropped up in cages widely scattered in the room. The entire room of animals was sacrificed to prevent spread to other rooms. The significance of these findings from an epidemiologic viewpoint is that *S. papillosus* is a common parasite of sheep, and sheep were introduced into the building five months before the outbreak. Five sheep were tested and found to be shedding ova.

Efforts to produce guinea pigs with limited microflora in the barrier facilities continued to be thwarted by fatal enterococcolitis and deaths of undetermined cause. As in rabbits, the enterococcolitis is caused, apparently, by imbalances of intestinal microflora.

Hemothorax continues to occur in relatively low incidence (6.9 percent of fatalities) in the barrier-maintained mouse colonies. As previously described, the disease appears to be a noninfectious condition of male mice characterized by myocarditis and prolonged bleeding time. In contrast to the first outbreak, which involved 10 to 12 week old GP mice, the disease is now recognized in all strains at four to six months of age. Efforts to reproduce the disease experimentally by feeding vitamin K deficient diets have been unsuccessful.

The major disease problems in nonhuman primates again were those which typically occur following shipment. In animals that died, 41.5 percent had colitis, usually hemorrhagic, and 26.2 percent had pneumonia. Bacteriologic studies indicated that the colitis was caused, for the most part, by Shigella sp.

Tyzzer's disease was found in only four rabbits, the lowest incidence in many years. This probably was the result of reduced colony size and the reestablishment of the colonies from cesarean-delivered stock in unusually clean quarters. Since its causative agent is a spore former, it is likely that the disease will become established in the colony again. A method to detect serum antibody to this disease using the indirect fluorescent antibody technique was developed, thus permitting more detailed studies of the natural history of the disease and its pathogenesis. Already it has been shown in limited studies that the agent in rabbits appears immunologically indistinguishable from the agent of Tyzzer's disease in foals. The latter agent was first isolated by CPS staff this year when assistance in dealing with a new disease of foals was urgently requested by the staff of the University of Kentucky.

Fecal culturing for Mycobacterium paratuberculosis in the goat herd was continued. The incidence of Johne's disease declined from 21 cases in 1972 to two in 1973. Culturing will continue for at least another year.

Initial screening of the sheep flock for Q fever was completed. None of the 71 sheep tested were considered to have active Coxiella burnetii infection. Testing will be performed on a continuing basis.

Brucellosis testing was continued in the swine herd, and no new cases were detected. Testing will be continued for about six months. Thereafter, only new acquisitions will be tested during the quarantine period.

Urolithiasis was diagnosed in 15 goats (wethers). Four of the cases were fatal. The disease is thought to be associated with the exclusive feeding of grain concentrates.

b. BID Animal Health Problems

The most serious animal disease problem in the NIH laboratories was an outbreak of ectromelia (mouse pox), the second such outbreak in NIH history. The first occurred in 1960. This disease is highly contagious and is feared in animal colonies and research laboratories because of the difficulty in eradication and because both the enzootic and epizootic forms of the disease wreak havoc with animal experimentation. This disease was introduced into an animal room in the NCI's Building 37 in mice received from England. Those mice are believed to have been infected just before shipment to the USA when they were inoculated with tumor cells contaminated with the causative virus. Fortunately, within several weeks after the mice were received at NIH, warning came from England that they might be infected. In brief, the affected area in Building 37 was placed under quarantine, the diagnosis was confirmed by serology and virus isolation, the infected and known exposed animals were

sacrificed, a large number of mice housed nearby were vaccinated, a serologic monitoring program was initiated. A variety of other measures were taken to prevent the virus from leaving Building 37 in animals or on inanimate fomites. No new cases of mouse pox have been detected since the disease was discovered. As a result of the outbreak, the NIH's policies governing the importation of mice and products of mice, including tumors, are undergoing revision.

Salmonellosis was introduced into a room of guinea pigs in the National Institute of Dental Research (NIDR) in a shipment of Hartley guinea pigs from a commercial supplier. After the animals were received, NIDR was notified by the supplier that the animals might be infected. The guinea pigs were cultured and found to be infected with a Group B Salmonella sp. The animals were sacrificed. Thirty-one of the 100 cages of inbred guinea pigs in the same room were cultured and found negative. Follow-up testing was recommended, but has not yet been solicited.

11. Animal Disease Investigation Service

The Animal Disease Investigation Service was reorganized during the year to insure rapid response to requests. The number of calls made to the BID increased by 22 percent, from 150 to 183. These involved consultative, diagnostic, and therapeutic activities. Animal species encountered were varied including rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls also varied and involved all Institutes. This service, well received by the BID investigators, gradually increased in scope. It has been mutually beneficial to investigators and to the VRB professional staff in providing an overview of laboratory animal facilities and practices at NIH.

D. Problems

Problems of Animal Disease are referred to in Part II, C, 10, a and b.

There is a serious understaffing problem in spite of contracts initiated to reduce in-house production. Some sections are forced to rely on temporary employees to meet the work load. Temporary employees are concentrated in the cagewash unit of the Small Animal Section, creating severe shortages when they are terminated in June. As a result of the manpower shortage, many employees are required to work unreasonable overtime and several necessary activities, such as increased inbred mouse production, were postponed.

There was a large revolving fund deficit for rodent and rabbit production. This indicates the need for financing research and development, strain development, and genetic repository activities from sources other than animal issues.

The contract supplier of Hartley guinea pigs was unable to supply animals to meet many requests by investigators. The colony was sold to another firm in the middle of the contract term. The original supplier was obliged to comply with the contract and continue production to meet NIH demands, but was usually unable to deliver animals requested.

A VRB employee retired on disability with emphysema which was claimed to be aggravated by the use of peracetic acid for disinfection of isolators and germfree equipment. Precautions are now taken to minimize exposure of employees doing germfree work to peracetic acid.

Lack of adequate space for personnel and for efficient utilization of equipment continues to be the major problem facing the Media Unit. In spite of several attempts to renovate existing space, overcrowding prevents necessary expansion in media storage at cold room temperatures and further automation of tubing, bottling, and plate pouring operations. The increase in volume and complexity of individual requests for media makes additional space mandatory if these demands are to be met without greatly increased backlogs in production.

Shortages of some material and supplies used daily in media production, and brought on by current shortages caused problems of varying degree. Agar supplies, for instance, have become very erratic and have made changes in production necessary to cope with the situation.

The supply of membrane filters for sterilization of tissue culture media has become a problem due to difficulties in meeting the justification required by procurement for a membrane fulfilling the specifications needed for media production.

The unit continued to have difficulty in supplying the daily demands for glassware trays for return of dirty glassware. Periodic repeat orders of 300 new trays seem to relieve the situation for short periods of time, but demand still exceeds supply. During FY 1973 and 74, 600 new trays were put into the system and plans to add 300 more trays are now being made.

Transportation of glassware to the outlying buildings and return of dirty glassware for processing continues to be a problem. Irregular pickups of dirty glassware causes needless fluctuations in work load; some days almost no glassware is returned and on other days there is too much to be processed efficiently. On slow days new glassware must be placed into circulation to meet demands when a more regular rate of return might conceivably lessen the need for endless supplies of new glassware. Recent publicity regarding the impact of the energy crisis on disposable types of glassware and plastic labware hopefully will increase awareness of researchers and elicit more cooperation.

Availability of quality, blood group CEA 1, 2, & 3 negative, microfilaria negative, dysplasia-free dogs as additions to the breeding colony will continue to be extremely limited. The rigid selection requirements retard full development of the breeding colony.

The sheep flock (donors and stock animals) is restricted from expanding to meet overall BID requirements because of the increasing numbers of sheep being housed for NHLI and NICHD programs. While the vast majority of the NHLI flock is maintained under contract at Luray, Virginia, the NIHAC provides short-term housing for a substantial and increasing number of sheep coming from or returning to the contractor and Bethesda.

While there appears to be a real need to provide facilities for breeding and holding swine, the BID's involved failed to provide sufficiently detailed POR's to enable the Section to formulate plans to meet the requirements.

Establishment of two large pasture areas for goat and burro breeding is behind schedule due to design and contracting problems.

While the supply of rhesus monkeys from India remained constant through FY 1974, difficulties were experienced in obtaining adult females suitable as breeders. It was, therefore, necessary to purchase large stock (3.7 to 4.6 kg) rhesus monkeys which are in reality subadults. Only 25 to 30 percent of the animals received are eventually selected as potential breeders, however, because each shipment of monkeys consists of 50 percent males and 20-25 percent of the females are unsuitable. Consequently, in order to provide the Perrine breeding colony with 500 potential breeders (females), more than 2,000 monkeys must be processed. It has also been found necessary to condition large stock monkeys for 90 to 120 days prior to shipping to Perrine or issuing to BID's. As a result, space for quaranting small stock rhesus monkeys was restricted, and some BID's were required to use large instead of small monkeys.

Contract prices for a variety of animals and products increased. The cost of random source foxhounds increased by a modest 4 percent, that of random source cats increased by 19 percent, and monkey costs increased by 30 percent for small and 36 percent for large stock rhesus. Feed costs escalated by 30 percent for dog food, 20 percent for livestock grain concentrates and 10 percent for monkey chow.

E. Program Plans

The program to free all rodent strains and stocks of disease through hysterectomy derivation will continue. Improved techniques will be developed for applying this practice to guinea pigs and rabbits. This requires a cooperative effort in areas of nutrition, microbiology, and genetics and development of methods for hand and foster nursing these species and for acclimating the animals to a pathogen-free environment.

An effort will be made to survey requirements of investigators for rodents beyond the capability of in-house production and to initiate new contracts to meet these needs, using VRB colonies as the genetic base. An improved quality control program for contract animals will be initiated. New strains of rodents will be added to the repository that have significant potential for research. The National Research Council has been asked to establish criteria for evaluating the importance of maintaining each new strain.

Studies to define the major nutrient requirements of different species and strains of inbred rodents will continue. It is essential to the establishment of SPF colonies of rabbits and guinea pigs that the present autoclavable rations for these species be improved.

Availability of feed ingredients presently used in formulation of laboratory animal rations is a major concern. Accordingly, studies to evaluate some lower quality, more readily available ingredients will be developed.

Efforts will continue to develop open formula rations purchaseable through advertised contracts to replace closed formula rations purchased through negotiated, sole source contracts.

Continued expansion of the canine breeding colony by purchase of quality dogs will be pursued. The feline breeding colony was relocated from Building T-8 to Building 102. This move provides sufficient space in the former location to house a total of 160 bitches and their progeny. Contract production of purebred foxhound puppies (approximately 600 per year) will be continued.

The dairy goat and burro breeding herds will be expanded during FY 1975 or as soon as appropriate fencing is installed around existing pasture land and shelters are erected.

Further definition of the blood groups of dogs in the canine donor and breeding colonies will be undertaken when "typing" antisera becomes available from outside sources.

The feline breeding colony (approximately 20 cats) will fill special requests for defined cats, timed-pregnancies, and neonates.

Emphasis on supplying the Perrine facility with a full complement of rhesus monkey breeding stock will continue. Anticipated achievement of this objective is mid-FY 1975, when the NIHAC program will be readjusted to provide holding space for young monkeys produced by the Perrine facility, and for conditioning replacement breeding stock for both Perrine and contractor(s).

Leasing 200 acres of pasture and several buildings adjacent to the Animal Center will provide space for sheep, swine, and burros. Improvement of existing structures, installation of fences and purchase of temporary farrowing/swine holding buildings must be vigorously pursued if effective use is to be made of the property during FY 1975.

In order to meet the increasing demands of the research community in the face of manpower reductions, continued efforts will be made to expand or improve automation. Improvements in the area of plate production of solid media are needed to keep pace with increasing demand for this service.

Continued efforts to expand quality control testing of all media will be concentrated in the area of automated testing of such parameters as glucose content, sodium ion concentration, etc. Extension of quality control testing to more bacteriologic media is planned as personnel and space needs are met.

A concerted effort to locate a supplier of deionized water will be made this year. Due to manpower reductions, it is no longer possible for Glassware Unit personnel to keep up with the constant regeneration of the large mixed bed deionizers.

The total impact of the energy shortage on plastic and disposable laboratory glassware is unknown and, therefore, its effect on program planning is difficult to predict. It seems logical that despite the promising immediate outlook for continued supplies, eventual shortages may occur.

Plans are underway to design and implement a new form for glassware issue to eliminate unnecessary paper work, provide information as to quantities and types of glassware issued and a record of glassware ordered for the requestor. Present methods do not give any permanent record of orders received.

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Serial No. DRS-VRB-1

1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973 through June 30, 1974

Project Title: PATHOLOGY OF ADJUNCTIVE EFFECT OF IMMUNOSUPPRESSION AND
THYMECTOMY ON CANINE PULMONARY ALLOGRAFTS

Previous Serial Number: DRS-VRB-3

Principal Investigator: Dawn G. Goodman

Other Investigators: Richard Scott, NHLI
Tom Bowles, NCI
Glenn Gaelhold, NCI
Paul Chretien, NCI
Thomas Moore, DRS

Cooperating Units: Surgery Branch, NCI
Special Programs and Resources Branch, NHLI

Man Years:

Total:	1.0
Professional:	.5
Others:	.5

Project Description:

Objectives: To evaluate the role of thymectomy on decreasing the immune response using the K-9 lung allograft as a model.

Methods Employed: Dogs which are 4 years or older and weighing 15 kg. or more are used. Fifteen dogs have been thymectomized as puppies. Four groups of dogs are used:

1. Controls--no immunosuppression or thymectomy
2. Standard immunosuppression (prednisone and azothioprine)
3. Standard immunosuppression plus thymectomy (performed at age 4-6 months).
4. Thymectomy without immunosuppression.

Major Findings: There are difficulties with surgical techniques and post-operative survival, particularly with the thymectomized dogs, which necessitate using larger numbers of dogs than previously anticipated.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-2

1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973 through June 30, 1974

Project Title: DIFFERENT LEVELS OF DIETARY PROTEIN FOR LABORATORY RATS

Previous Serial Number: DRS-VRB-4

Principal Investigators: Anton M. Allen
Joseph J. Knapka

Other Investigator: K.P. Smith

Cooperating Units: Comparative Pathology Section, VRB, DRS

Man Years:

Total:	1.0
Professional:	.5
Other:	.5

Project Description:

Objectives: To evaluate the effect of various levels of dietary crude protein on the reproductive performance, various physiological systems, pathology and longevity of noninbred stocks of rats.

Methods Employed: A series of factorial designed, long-term feeding trials are conducted involving rations containing various concentrations of crude protein. Throughout the study various reproductive trials and physiological determinations are recorded. At predetermined intervals, rats from each treatment group are sacrificed for pathological evaluation.

Major Findings: Evaluation of reproductive data has shown a decrease in the level of dietary protein from 24 to 16 percent had no significant effect on the number of offspring weaned. Analyses of pathological data are presently in progress.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-3

1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973 through June 30, 1974

Project Title: GENETIC ANALYSIS AND ANIMAL MODEL DEVELOPMENT

Previous Serial Number: DRS-VRB-5

Principal Investigator: C.T. Hansen

Other Investigators: K.P. Smith
W.J. Hinkle
W.J. McEleney

Cooperating Units: Laboratory of Bacterial Products, BoB
Laboratory of Immunology, NIAID
Laboratory of Pathology, GLC, NCI

Man Years:

Total:	1.0
Professional:	.5
Others:	.5

Project Description:

Objectives: 1) To study the role of genetic and environmental components involved in the dynamics of reproductive performance of inbred strains of animals, 2) genetic monitoring of inbred strains, and 3) develop new animal models utilizing the existing gene pool and new and exotic species.

Methods Employed and Major Findings: Comparisons of reproductive performance of 17 inbred strains of rats between conventional and SPF conditions show a 20 percent average increase in the SPF environment over that of the conventional environment. The major difference between the two environments was a marked reduction in neonatal loss in the SPF environment.

A study has been undertaken to determine if genetic variation still exists within long inbred strains of mice. The response to selection for increase in body weight between three and six weeks of age was compared in progeny produced by inbreeding and outbreeding within two inbred strains and one outbred stock. Sufficient results have not yet been accumulated to indicate any significant results.

Comparison of tumor frequencies between conventional and SPF inbred strains suggests for the most part that establishing these animals in an SPF

environment does not affect either the age of onset or frequency. One exception has been in the C3H/HeN strain in which the appearance of mammary tumors occurs at a somewhat earlier age and the growth of the tumor is more rapid.

The genetic analysis of blood pressure continues. Measurements in the 19 inbred strains of rats show almost a normal distribution of blood pressures suggesting a complex form of inheritance. A series of diallel crosses between a number of these strains show a marked sex difference in the pattern of inheritance. In female progeny, the evidence suggests an additive form of inheritance whereas in males, the inheritance appears to be nonadditive.

Selected breeding for the sensitivity and resistance to the effect of histamine after treatment with B. pertussis has reached the fifteenth generation. Sensitivity has increased to 85 percent in the sensitive strains and decreased to 3-5 percent in the resistant strain from an average sensitivity of 30 percent in the unselected base population.

A program has been undertaken to develop a mating system for the maintenance of outbred SPF nucleus colonies of mice and rats. The goal of this program is to develop a system which meets the requirements for maintaining a stable gene frequency, minimize inbreeding and reduce the requirement for close professional supervision. Several revisions have been made during the course of this program and the present technique appears to be successful in meeting the majority of the requirements.

A long-term study with the nude (athymic) mouse has been established. This animal is very unique in that the thymus fails to develop with the result that half of the immune mechanism is absent. The potential of this animal for immunological and cancer research is considerable. The project consists of two phases. First, to develop techniques and procedures for large-scale production since it is extremely susceptible to various infections. Second, to establish this gene on a number of inbred strains to study the effect that the absence of the thymus mediated immune system has on established immune responses and tumor frequencies of these inbred strains.

Significance: The significance of these projects is to develop, by the use of genetic procedures, new animal models which have an application to biomedical research.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-4

1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973 through June 30, 1974

Project Title: DEVELOPMENT OF DIETS FOR LABORATORY ANIMALS

Previous Serial Number: DRS-VRB-6

Principal Investigator: J.J. Knapka

Other Investigators: F.J. Judge
K.P. Smith

Cooperating Units: None

Man Years:

Total:	2.0
Professional:	.5
Others:	1.5

Project Description:

Objectives: 1) To formulate and evaluate open formula rations designed to improve the nutritional status of laboratory animal colonies, 2) to accumulate data regarding the specific nutrient requirements of various strains of inbred laboratory rodents.

Methods Employed: A series of factorial designed feeding trials are conducted to determine the effect of various diets differing in nutrient concentrations and physical form on the growth and reproductive performance of the species involved. Criteria of evaluation include number of pregnancies, number of offspring weaned, weight of offspring weaned, and the post-weaning, growth rate of offspring. These data are coded for computer analysis by the appropriate statistical methods.

Major Findings: Data have accumulated which indicate differences in crude protein and crude fat requirements between various strains of inbred mice. These data also show reproduction is not affected when the dietary crude protein level is reduced from 24 to 8 percent. A significant protein x fat interaction indicated maximum reproduction in mice colonies is dependent on the dietary ratio of these major nutrients rather than the concentration of each nutrient per se.

The problems associated with ascorbic acid stability in autoclavable open formula guinea pig rations appear to be resolved. Guinea pigs have been

maintained on these rations for up to six months without showing any clinical signs of scurvy. Considerable progress has been made in the development of autoclavable open formula rations for rats, mice, and rabbits.

Significance: The development of open formula rations for NIH production and research animal colonies is advantageous because 1) production of rations is not restricted to a single mill in the event of a fire or bacterial contamination, 2) investigators have the opportunity to know the complete nutritional status of animal colonies, 3) a basis is provided for the improvement of rations for particular stocks or strains of animals, and 4) competitive procurement of essentially the same product can be accomplished over many years.

The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved if rations can be developed that supply nutrients in concentrations nearly equal to the requirements of the strain of animal involved.

Proposed Course: Continuation

Honors and Awards: None

Publications: Knapka, J.J. and Judge, F.J.: The Effects of Various Levels of Dietary Fat and Apple Supplementation on Growth of Golden Hamsters (Mesocricetus auratus). Lab. Anim. Sci. 24: 318-325, 1974.

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Serial No. DRS-VRB-5

1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973 through June 30, 1974

Project Title: TYZZER'S DISEASE

Previous Serial Number: None

Principal Investigator: James R. Ganaway

Other Investigators: Anton M. Allen
Thoms D. Moore

Cooperating Unit: University of Kentucky (Dr. T.W. Swerczek)

Man Years:

Total:	1.0
Professional:	1.0
Others:	.0

Project Description:

Objectives: To characterize the etiologic agent. To study the pathogenesis of the disease through experimental transmission studies. To recommend measures for the control and/or prevention of the disease.

Methods Employed: Microbiology and pathology.

Major Findings: The disease continues to occur enzootically in the NIH rabbit production colony. Studies designed to elucidate the biology of the etiologic agent, Bacillus piliformis, continue. We have confirmed the diagnosis of Tyzzer's disease in foals, this being the first knowledge of the spontaneous occurrence of this fatal disease in this species (collaborative studies with Dr. Hall, University of Connecticut and Dr. Swerczek, University of Kentucky). We have isolated the agent from the liver of a foal which died of the disease. The developmental and morphologic properties are similar to the agent isolated from laboratory rabbits with Tyzzer's disease. Serological studies using the fluorescent antibody technique indicate that the isolants from each of these two divergent species are closely related if not identical.

Significance: This disease was known to occur only in laboratory mice prior to 1965. As a result of our having described this disease in epizootic form in the NIH laboratory rabbit colony and, further, by providing basic criteria necessary for diagnosis, the disease is presently recognized as a major cause of epizootic fatal disease in rats, mice, hamsters, gerbils, rabbits, cats, muskrats, wild hares, subhuman primates, and horses. Tyzzer's disease is

recognized as one of the major diseases of laboratory animals which complicates and interferes with biomedical research.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-6

1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973 through June 30, 1974

Project Title: A COMPARISON OF THE EFFECTIVENESS OF SUTURE MATERIALS ON
BRONCHIAL STUMP CLOSURE FOLLOWING PNEUMONECTOMY

Previous Serial Number: None

Principal Investigator: Richard Scott, NHLI

Other Investigators: Dawn G. Goodman
Glenn Gaelhold, NCI
Paul Chretien, NCI

Cooperating Units: Surgery Branch, NCI
Special Programs and Resources Branch, Division
of Lung Diseases, NHLI

Man Years:

Total:	0.5
Professional:	.25
Other:	.25

Project Description:

Objective: To compare the effect of three types of suture material: silk, chromic gut, and wire staples on closure of the bronchial stump following pneumonectomy.

Methods Employed: Random source dogs are used. Pneumonectomies are performed and the bronchial stump is closed with either silk, chromic gut, or wire staple sutures. The dogs are sacrificed 14 days postoperatively. The tensile strength of the suture line is evaluated. Then the bronchial stump is cultured for bacteria and evaluated histopathologically.

Major Findings: Histopathologically, the wire staples were found to cause very little tissue reaction, the chromic gut to be intermediate and the silk to cause the most severe reaction at 14 days postoperatively. However, all three were equally effective in obtaining adequate closure of the bronchial stump.

Significance: Suture materials have never been evaluated with regard to closure and healing in the bronchi.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-7

1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973 through June 30, 1974

Project Title: SELECTION FOR 6-WEEK WEIGHT IN INBRED AND
NONINBRED STRAINS OF MICE

Previous Serial Number: None

Principal Investigator: K.P. Smith

Other Investigator: C.T. Hansen

Cooperating Units: None

Man Years:

Total:	1.0
Professional:	.5
Others:	.5

Project Description:

Objectives: To determine if a significant amount of genetic variation still exists within highly inbred strains of mice.

Methods Employed: The design includes three strains of mice--two inbred (C3H+/HeN and NGP) and one noninbred (GP). There are 72 mating pairs per strain. In each strain there are three groups: 1) 12 pair of brother x sister matings, 2) 24 pair of random matings, 3) 36 pair of random matings which are selected for six-week body weight. The experiment will include six generations.

Major Findings: Only the first generation has been completed.

Significance: If it can be demonstrated experimentally that all of the genetic variation in a quantitative trait such as six-week body weight has been eliminated from highly inbred strains, it should be possible to simplify the mating systems used and reduce production costs.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-8

1. Veterinary Resources Branch
2. Veterinary Medicine and Surgery Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1973 through June 30, 1974

Project Title: SODIUM CYANATE NEUROTOXICITY IN MACACA NEMISTRINA PRIMATES

Previous Serial Number: None

Principal Investigator: David K. Johnson

Other Investigators: Robert A. Whitney, Jr.
French Anderson, NHLI

Cooperating Units: Section on Molecular Hematology, NHLI

Man Years:

Total:	0.6
Professional	.3
Others:	.3

Project Description:

Objectives: Sodium cyanate is a potential chemotherapeutic agent for treating sickle cell anemia in humans. This study will evaluate alleged central neurological lesions caused by sodium cyanate in Macaca nemestrina.

Methods Employed: Twelve pig-tail monkeys, Macaca nemestrina will be given deep intramuscular injections of sodium cyanate, four animals will receive sham injections, and four control animals will receive no injections. The total duration of the study will be 4 months. Following the test period, all animals will be humanely killed and perfused for neuropathological examination. During the course of the experiment, routine blood samples will be taken for hematological/serum chemistry evaluations which will be based on pre-experimentation baseline data.

Major Findings: Currently unknown.

Proposed Course: Completion by June 1974.

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-9

1. Veterinary Resources Branch
2. Veterinary Medicine and Surgery Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1973 through June 30, 1974

Project Title: ERYTHROCEBUS PATAS MONKEY AS AN ANIMAL
MODEL FOR CARDIOVASCULAR RESEARCH

Previous Serial Number: DRS-VRB-1

Principal Investigator: David K. Johnson

Other Investigators: Donald L. Fry, NHLI

Cooperating Units: Section on Experimental Atherosclerosis,
ODIR, NHLI

Man Years:

Total:	0.3
Professional:	0.2
Other:	0.1

Project Description:

Objectives: 1) To determine the suitability of the patas monkey for atherosclerotic studies as they relate to humans. Positive findings would provide an animal model from an African source which could have better availability than Asian primates, and 2) To determine whether the patas monkey has advantages as an animal model for cardiovascular studies over those species presently available.

Methods Employed: Fifty patas monkeys (Erythrocebus patas) were purchased and maintained on monkey chow for 4 months while base line data was obtained. They were then randomly divided into one group of 10 animals and two groups of 20. The group of 10 received monkey chow, one group of 20 received a semisynthetic diet with high fat and low cholesterol levels. The other group of 20 received a high fat and high cholesterol semisynthetic diet. Monthly blood samples are being drawn and a variety of hematological, serum chemical, and serum lipid data are being obtained.

Major Findings: The test group of 20 patas monkeys in the high fat-low cholesterol diet had a rapid rise in their serum lipid profile which is persisting while being fed the atherogenic diet. The serum lipid profiles of the patas monkeys on the high fat-low cholesterol diet patterned the serum lipid profiles of the monkeys being fed the monkey chow, which is not varying

from their baseline data. After 12 months on the test diets, one-half of each group was humanely killed and necropsies performed, with emphasis placed on the cardiovascular system. Atherosclerotic lesions were evident in the high fat-high cholesterol group in contrast to the other two groups. Further evaluations are in progress.

Proposed Course: The balance of the patas monkeys are being maintained on the prescribed diets for a total of 24 months. Serum lipid fractionations are being accomplished to determine if the types and changes in lipid components are comparable to human atherosclerosis. Further definition is needed relative to lower cholesterol diet levels, exercise, hypertension, and other variables. Continued studies employing patas monkeys are forecasted as they show definite promise as a useful animal model for comparative atherosclerosis.

Honors and Awards: None

Publications: None







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